

Lower Extremity Arterial Disease

EDITED BY

Dennis G. Caralis,

MD, PhD, MPH, FACC, FAHA

George L. Bakris,

MD, FACP, FAHA, FASN

 HUMANNA PRESS

LOWER EXTREMITY ARTERIAL DISEASE

CLINICAL HYPERTENSION AND VASCULAR DISEASES

WILLIAM B. WHITE, MD
SERIES EDITOR

- Lower Extremity Arterial Disease*, edited by Dennis G. Caralis, MD, PhD, MPH, FACC, FAHA and George L. Bakris, MD, FACP, FAHA, FASN, 2005
- Secondary Hypertension: Clinical Presentation, Diagnosis, and Treatment*, edited by George A. Mansoor, MD, 2004
- Pediatric Hypertension*, edited by Ronald J. Portman, MD, Jonathan M. Sorof, MD, and Julie R. Ingelfinger, MD, 2004

LOWER EXTREMITY ARTERIAL DISEASE

Edited by

DENNIS G. CARALIS, MD, PhD, MPH, FACC, FAHA

*Department of Medicine, Section of Cardiology
Rush University Medical Center, Chicago, IL*

and

GEORGE L. BAKRIS, MD, FACP, FAHA, FASN

*Department of Medicine, Division of Nephrology
Rush University Medical Center, Chicago, IL*



HUMANA PRESS
TOTOWA, NEW JERSEY

© 2005 Humana Press Inc.
999 Riverview Drive, Suite 208
Totowa, New Jersey 07512

humanapress.com

For additional copies, pricing for bulk purchases, and/or information about other Humana titles, contact Humana at the above address or at any of the following numbers: Tel.: 973-256-1699; Fax: 973-256-8341, E-mail: humana@humanapr.com; or visit our Website: www.humanapress.com

All rights reserved.

No part of this book may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, microfilming, recording, or otherwise without written permission from the Publisher.


All articles, comments, opinions, conclusions, or recommendations are those of the author(s), and do not necessarily reflect the views of the publisher.

Due diligence has been taken by the publishers, editors, and authors of this book to assure the accuracy of the information published and to describe generally accepted practices. The contributors herein have carefully checked to ensure that the drug selections and dosages set forth in this text are accurate and in accord with the standards accepted at the time of publication. Notwithstanding, as new research, changes in government regulations, and knowledge from clinical experience relating to drug therapy and drug reactions constantly occurs, the reader is advised to check the product information provided by the manufacturer of each drug for any change in dosages or for additional warnings and contraindications. This is of utmost importance when the recommended drug herein is a new or infrequently used drug. It is the responsibility of the treating physician to determine dosages and treatment strategies for individual patients. Further it is the responsibility of the health care provider to ascertain the Food and Drug Administration status of each drug or device used in their clinical practice. The publisher, editors, and authors are not responsible for errors or omissions or for any consequences from the application of the information presented in this book and make no warranty, express or implied, with respect to the contents in this publication.

Production Editor: Nicole E. Furia

Cover design by Patricia F. Cleary

Cover Illustration: Figure 3D from Chapter 2, "Noninvasive Diagnostic Evaluation of Peripheral Arterial Disease," by Nicos Labropoulos and Apostolos K. Tassiopoulos.

This publication is printed on acid-free paper. 

ANSI Z39.48-1984 (American National Standards Institute) Permanence of Paper for Printed Library Materials.

Photocopy Authorization Policy:

Authorization to photocopy items for internal or personal use, or the internal or personal use of specific clients, is granted by Humana Press Inc., provided that the base fee of US \$30.00 per copy is paid directly to the Copyright Clearance Center at 222 Rosewood Drive, Danvers, MA 01923. For those organizations that have been granted a photocopy license from the CCC, a separate system of payment has been arranged and is acceptable to Humana Press Inc. The fee code for users of the Transactional Reporting Service is: [1-58829-554-0/05 \$30.00].

Printed in the United States of America. 10 9 8 7 6 5 4 3 2 1

eISBN 1-59259-881-1

Library of Congress Cataloging-in-Publication Data

Lower extremity arterial disease / edited by Dennis G. Caralis and George L. Bakris.

p. ; cm. — (Clinical hypertension and vascular diseases)

Includes bibliographical references and index.

ISBN 1-58829-554-0 (hardcover : alk. paper)

1. Leg—Blood-vessels—Diseases. 2. Arteries—Diseases.

[DNLM: 1. Vascular Diseases—diagnosis. 2. Vascular Diseases—therapy.

3. Arteries—physiopathology. 4. Lower Extremity—physiopathology. WG 510

L917 2005] I. Caralis, Dennis G. II. Bakris, George L., 1952- III. Series.

RC694.L685 2005

616.1'3—dc22

2004013537

SERIES EDITOR'S INTRODUCTION

The morbidity of peripheral arterial disease and its associated co-morbidities are becoming increasingly recognized by physicians and scientists in the 21st century. Drs. Caralis and Bakris' volume on *Lower Extremity Arterial Disease* is an up-to-date and clinically relevant contribution to the field of arterial disorders that brings together the numerous pathophysiologic, diagnostic, and therapeutic advances in the evaluation of atherosclerosis and peripheral arterial diseases involving the lower extremities.

The editors have carefully organized their volume into sections that detail the epidemiology of arterial disorders as it relates to smoking, diabetes, and hypertension as risk factors. There is ample coverage of diagnostic testing for claudication and lower extremity arterial disease using both noninvasive and arteriographic techniques. A superb chapter on the pathogenesis of arteriosclerosis using a translational approach segues the sections on diagnosis and epidemiology with those on treatment and special patient populations.

The editors have four chapters devoted to the management of claudication and lower extremity arterial disease: nonpharmacological (exercise), medical therapy, angioplasty, and endovascular stent placement and revascularization. These comprehensive chapters are very clinically oriented and help the reader to understand when nonsurgical versus surgical management should be considered.

The chapters in *Lower Extremity Arterial Disease* have been written by several well-known authors who have provided comprehensive, scientifically sound, and clinically appropriate information. As series editor of *Clinical Hypertension and Vascular Diseases*, I am delighted by this timely and excellent book and know that *Lower Extremity Arterial Disease* will become a highly useful textbook for all physicians interested in arteriosclerosis, diabetes, vascular medicine, interventional radiology, and general and vascular surgery.

William B. White, MD

Series Editor

PREFACE

Arterial diseases are the leading causes of morbidity and mortality in all industrialized countries, and their incidence is increasing in non-industrial countries. Among the industrialized countries, the United States in particular is in the midst of an epidemic of obesity and diabetes. One in four Americans meets the criteria for obesity and the number keeps growing.

Lower Extremity Arterial Disease (LEAD) is a common disease entity for men older than 40 and women older than 50 years of age. The prevalence of LEAD continues to increase with age, from less than 3% in the population younger than the age of 60 to more than 20% at age 75 and older. The majority of patients older than 75 with LEAD are asymptomatic. Prevention of arterial disease is key to reducing morbidity and mortality. LEAD is associated with specific risk factors, namely hypertriglyceridemia, homocysteinemia, very low HDL cholesterol, physical inactivity, and above all cigaret smoking and diabetes mellitus, alone or in tandem.

LEAD, symptomatic or not, particularly when it coexists with Coronary Artery Disease (CAD) (Chapter 9), calls for polypharmacy. Polypharmacy should no longer have a bad connotation in treating patients with LEAD and CAD. In patients with metabolic syndrome and LEAD, a short-acting statin in the evening and triglyceride-reducing fenofibrate during breakfast can improve time to claudication significantly, improve endothelial function, improve the lipid profile, and at the same time decrease the probability of a coronary event. Fenofibrate and rosuvastatin or simvastatin should be given twelve hours apart to avoid an overlap of their half-lives. In treating LEAD, aggressive risk factor modification should be implemented, which includes: smoking cessation, euglycemic control of diabetes, ideal control of both systolic and diastolic pressure, dramatic improvement of the lipid profile, low calorie Mediterranean diet rich in antioxidants, and, equally important, exercise therapy, either community based or supervised (Chapter 11).

Percutaneous interventions with balloon angioplasty, bare metal stents, and the more preferable for the femoral and intrafemoral arteries, drug-diluting stents, offer dramatic improvement of the stenosed or occluded lumen (Chapter 12). Blood flow is restored and great symptomatic relief is achieved. Arterial grafting techniques have also pro-

vided tremendous advances in reinstating peripheral blood flow with the lowest possible periprocedural complication rate. Today's therapeutic armamentarium also includes the most promising approach for advanced and distal disease (i.e., therapeutic angiogenesis). The vascular growth factors can be administered intra-arterially or intramuscularly in the ischemic muscle. Therapeutic angiogenesis combined with the other current therapeutic options and aggressive risk-factor modification can remarkably improve claudication, prevent limb loss, and prolong life (Chapters 10 and 13).

The presence of LEAD, as defined by an ankle brachial index (ABI) of less than one, adversely influences the prognosis of coronary heart disease. The lower the ABI (the lowest in either ankle), the worse the prognosis. The morbidity and mortality from coronary artery bypass grafting is higher in patients with LEAD. The same increased morbidity and mortality also occurs during or after percutaneous coronary interventions, short or long term. LEAD differs from other peripheral arterial diseases by its specific medical therapy as well; the drug currently approved by the Food and Drug Administration to treat the symptoms of claudication, the phosphodiesterase III inhibitor Cilostazol, has no effect on other arterial beds like the renal or the carotid systems (Chapter 10).

Intermittent claudication can be caused by an abdominal aortic aneurysm (AAA), which is a totally different disease entity with different pathophysiology and distinct genetic mechanisms. AAAs cannot be stopped from increasing in diameter with either blood pressure control or antilipid therapy.

Lower Extremity Arterial Disease provides a comprehensive state-of-the-art review of LEAD. A detailed review of its cardinal symptom, intermittent claudication, is presented in Chapter 1. The book provides a thorough and detailed description of noninvasive and accurate assessment of LEAD with special emphasis on the ABI and its diagnostic and prognostic significance. Modern diagnostic methods, such as vascular flow patterns and magnetic resonance angiography, are eloquently presented for the educational benefit of the clinician in Chapter 2. The known risk factors for LEAD and CAD—smoking, diabetes mellitus, dislipidemia, systemic hypertension, and physical inactivity—are presented in the chapters on epidemiology and risk factors (Chapters 3–8).

The question "What do claudiants die from?" is reviewed and analyzed in the chapter on LEAD coexisting with CAD. The presence of LEAD increases significantly the probability of coexisting CAD. In patients who cannot exercise much because of claudication or in asymptomatic patients with LEAD, the preferred approach to diagnose coex-

isting CAD is dual isotope pharmacological stress testing either with adenosine IV or dipyridomole IV. Adenosine should not be given if bronchial asthma, hypotension, or profound bradycardia is present. Alternatively, dobutamine can be utilized as a pharmacologic stressor. Dobutamine should not be used in patients with LEAD and atrial fibrillation; dobutamine remarkably accelerates atrioventricular conduction. Dobutamine should be avoided as a pharmacologic stressor if blood pressure is elevated; it may precipitate a hypertensive crisis. If the clinical index of suspicion is high, then the cardiovascular physician may recommend coronary angiography (luminography is a more accurate term). Overall, single photon emission computed tomographic images of the myocardium are preferable because they can accurately assess myocardium at risk in patients with LEAD.

In morbidly obese patients (those weighing more than 350 lbs) with LEAD, neither myocardial perfusion studies nor coronary angiography can be performed for technical reasons. These patients can be evaluated with contrast echocardiography (Chapter 9). The management of patients with LEAD and CAD is the same as in every patient who has myocardial ischemia, silent or symptomatic.

Dennis G. Caralis, MD, PhD, MPH, FACC, FAHA

George L. Bakris, MD, FACP, FAHA, FASN

CONTENTS

Series Editor's Introduction	v
Preface	vii
Contributors	xiii
1 Claudication: <i>Clinical Diagnosis and Differential Diagnosis</i>	1
<i>Dennis G. Caralis</i>	
2 Noninvasive Diagnostic Evaluation of Peripheral Arterial Disease	23
<i>Nicos Labropoulos and Apostolos K. Tassiopoulos</i>	
3 Smoking and Smoking Cessation	39
<i>Albert J. Bellg and Aristdis N. Mavridis</i>	
4 Peripheral Arterial Disease and Diabetes	53
<i>George L. Bakris</i>	
5 Hyperlipidemia in Peripheral Arterial Disease	61
<i>Ambika Babu, C. R. Kannan, and Theodore Mazzone</i>	
6 Hypertension and Peripheral Vascular Disease	75
<i>Anjula Gandhi, Jay Garg, and George L. Bakris</i>	
7 Physical Inactivity is a Risk Factor for Lower Extremity Arterial Disease and Coronary Heart Disease	85
<i>Dennis G. Caralis and Stamatis Dimitropoulos</i>	
8 Pathogenesis of Atherosclerotic Vascular Disease	99
<i>Bassem Jamil Basha, George L. Bakris, and James R. Sowers</i>	
9 Lower Extremity Arterial Disease Co-Existing With Coronary Artery Disease	183
<i>Dennis G. Caralis</i>	
10 Medical Therapy of Claudication and Lower Extremity Arterial Disease	223
<i>Dennis G. Caralis</i>	
11 Exercise Therapy for Lower Extremity Arterial Disease	243
<i>Peter F. Kokkinos</i>	

12	Endovascular Strategies for Management of Claudication and Lower Extremity Arterial Disease	257
	<i>Michael C. Brunner and Dennis G. Caralis</i>	
13	Severe Lower Extremity Arterial Disease: <i>Limb Salvage</i> <i>and Revascularization</i>	269
	<i>Chad E. Jacobs and Walter J. McCarthy</i>	
	Index	293

CONTRIBUTORS

- AMBIKA BABU, MD • *Division of Endocrinology, Cook County Hospital, Chicago, IL*
- GEORGE L. BAKRIS, MD, FACP, FAHA, FASN • *Division of Nephrology, Department of Medicine, Rush University Medical Center, Chicago, IL*
- BASSEM JAMIL BASHA, MD • *Division of Endocrinology, Department of Medicine, Harper University Hospital, Detroit, MI*
- ALBERT J. BELLG, PhD • *Cardiac Psychology Program, Appleton Heart Institute, Appleton, WI*
- MICHAEL C. BRUNNER, MD • *Department of Radiology, Swedish Covenant Hospital, Chicago, IL*
- DENNIS G. CARALIS, MD, PhD, MPH, FAHA • *Division of Cardiology, Department of Medicine, Rush University Medical Center, Chicago, IL*
- STAMATIS DIMITROPOULOS, MD • *Department of Medicine, Rush University Medical Center, Chicago, IL*
- ANJULA GANDHI, MD • *Department of Preventive Medicine, Rush University Medical Center, Chicago, IL*
- JAY GARG, MD • *Department of Preventive Medicine, Rush University Medical Center, Chicago, IL*
- CHAD E. JACOBS, MD • *Division of Vascular Surgery, Department of Cardiovascular–Thoracic Surgery, Rush University Medical Center, Chicago, IL and Stroger Hospital of Cook County, Chicago, IL*
- C. R. KANNAN, MD • *Department of Endocrinology, Cook County Hospital, Rush University Medical Center, Chicago, IL*
- PETER KOKKINOS, PhD, FACSM • *Veterans Affairs Medical Center and Georgetown University Medical Center, Washington, DC*
- NICOS LABROPOULOS, PhD, DIC, RVT • *Division of Vascular Surgery, Loyola University Medical Center, Maywood, IL*
- ARISTDIS N. MAVRIDIS, MD, FCCP • *United States Public Health Service Hospital, Baltimore, MD*
- THEODORE MAZZONE, MD • *Section of Diabetes and Metabolism, University of Illinois at Chicago, Chicago, IL*
- WALTER J. MCCARTHY, MD • *Section of Vascular Surgery, Department of Cardiovascular–Thoracic Surgery, Rush University Medical Center, Chicago, IL*
- JAMES R. SOWERS, MD • *Division of Endocrinology, Metabolism, and Hypertension, University Health Center, Detroit, MI and University of Missouri Medical Center, Columbia, MO*
- APOSTOLOS K. TASSIOPOULOS, MD • *Cook County Hospital, Chicago, IL*

1

Claudication

Clinical Diagnosis and Differential Diagnosis

*Dennis G. Caralis, MD, PhD, MPH,
FAHA, FACC*

CONTENTS

INTRODUCTION
CLAUDICATION IN THE ELDERLY
DIFFERENTIAL DIAGNOSIS
PSEUDOCLAUDICATION
VASOSPASTIC CLAUDICATION
REFERENCES

INTRODUCTION

Legend has it that the term *claudication* was given after the Roman Emperor Claudius, who would walk for a short distance, then stop and stand before he would start walking again. Etymologically, claudication is derived from the Latin verb *claudicare*, which means to limp. In 1858, Jean Martin Charcot described pain in the lower extremities resulting from arterial insufficiency. Intermittent claudication can inhibit walking, and cause limping due to ischemia of the lower extremity unilaterally or bilaterally. The most common cause of lower extremity ischemia is peripheral arterial disease of the major arteries supplying the legs and feet. Lower extremity ischemia may also progress to severe limb-threatening ischemia with symptoms and physical signs at rest as well. A detailed complete history should be obtained from every patient, middle-aged and the elderly, before the diagnosis of claudication is made. Vascular claudication under the age of 45 years is rare.

From: *Clinical Hypertension and Vascular Diseases: Lower Extremity Arterial Disease*
Edited by: D. G. Caralis and G. L. Bakris © Humana Press Inc., Totowa, NJ

Frequent symptoms of lower extremity arterial disease (LEAD) are pressure, tightness, squeezing sensation, burning, and frank pain precipitated by leg exercise and relieved by rest. Intermittent claudication also may be present as fatigue in working skeletal muscles. Continuous pain must be differentiated from intermittent pain, because continuous pain may be a result of a sudden arterial occlusion with or without pre-existing stenosis. Extremely severe ischemia or ischemic neuropathy, ulceration, or gangrene can also cause continuous pain.

Persistent pain of an extremity may have a different etiology other than arterial occlusive disease, from an atheromatous process or embolization. Connective tissue diseases with arteritis can cause persistent leg pain (1). Venous insufficiency, severe anemia, muscle phosphorylase deficiency, muscular dystrophy, radiation fibrosis, and retroperitoneal fibrosis have been associated with painful lower extremities (1,2). Ergot toxicity and cyclist's lesion may cause pain in the legs during exercise (2-4). (Ergotamine toxicity can also cause mitral valve disease [3] and coronary spasm.) Extra-arterial causes of persistent pain are phlebitis with or without phlebothrombosis and lymphangitis. Intermittent tightness or pain in a muscle group is more characteristic of intermittent claudication, and is generally associated with exertion. Rarely, claudicants may report worsening of the claudication when treated with β -blockers (5,6). In general though, β -blockers are safe in LEAD. If there is a definite indication for their use, they should be administered. They can cause reduction of the cardiac output and blockade of β 2-adrenoreceptor mediated skeletal muscle vasodilatation. The latter effect results in unopposed β -adrenoreceptor vasoconstriction. β -Blocking agents with β 1-selectivity (cardioselective) should be used instead in order to avoid the effects of peripheral vasoconstriction.

Intermittent claudication typically occurs with walking and is relieved with rest or standing. Location of the symptoms can be the hip, unilaterally or bilaterally, the thighs, the calf most frequently, and the foot. Claudication of the foot caused by ischemia is less common. It may exist independently of claudication of the calf when the occlusive lesions are diffuse and involve small arterial branches of the infrapopliteal arteries distally (4) such as in diabetic patients. A clinical clue to the diagnosis of frank claudication of the foot is its common association with more proximal arterial occlusions and calf pain. Claudication of the foot is usually manifested as pain or ache or a *catch* or a cramp in the forefoot precipitated by walking. More observant patients also report a more cold foot at night, ipsilaterally. Prognostically, claudication of the foot, as uncommon as it may be, indicates severe and diffuse atherosclerotic disease that frequently progresses to ischemic pain at rest. The posterior tibial pulse is virtually always absent (8-11).

Intermittent claudication is a clinical diagnosis. Usually lower extremity ischemia is caused by flow-limiting atherosclerotic plaques. Intermittent claudication is the presenting symptomatology in half of the patients with chronic lower extremity ischemia. The other one-third to half of patients with documented peripheral arterial occlusive disease are asymptomatic or silent (8). Other symptoms and physical findings indicating more severe ischemia are pain at rest, pale and cold extremity(s), ischemic ulcers, peripheral cyanosis, and gangrene (12).

Less frequently, peripheral symptoms may appear episodically as a result of an otherwise silent dissection of the aorta (4). Coarctation of the aorta, thoracic, or abdominal, is another cause of intermittent claudication (4,13). Episodic claudication can also be caused by distal embolization of a mural thrombus from the left cardiac ventricle or the left atrium, and less commonly from a left atrial or left ventricular myxoma. Because of its many clinical presentations cardiac myxoma has been described as the *great simulator* (14). The importance of atrial fibrillation as a cause of embolism is well known (15). Increasingly, recognized sources of emboli utilizing trans esophageal echocardiography are left atrial thrombi in patients with large left atria, atrial septal aneurysms, or fibrillating atria. Embolization from the heart can precipitate a dramatic symptomatology. Claudication can be a result of an aortic aneurysm or from an arterial aneurysm situated proximally to the site of the symptoms. An aneurysmal dilatation (16) or a significant ectasia can cause hemodynamically important limitation of blood flow and be the source of distal emboli as well. The prevalence of abdominal aortic aneurysms in older men varies from 0.4 to 5.4%. In carotid artery disease the prevalence of abdominal aortic aneurysms can be as high as 25.7% (17). Atherosclerosis can be a generalized disease.

The symptoms of claudication is a result of LEAD confirmed by ABIs or duplex scanning can be classified on a scale of I–IV, a grading classification of the Canadian Heart Association that parallels that of angina pectoris.

Claudication, Class I is hemodynamically significant LEAD diagnosed, either by physical examination, by arterial flow studies, or by ankle brachial indices but without symptoms.

Claudication, Class II is symptomatology precipitated by moderate exertion, e.g., walking fast or for a long distance or uphill and relieved by rest, usually standing.

Claudication, Class III is characterized by symptoms precipitated by walking on a straight level and for a short distance, the equivalent of one to two city blocks, approximately 50–100 m.

Claudication, Class IV is ischemic pain of one or both lower extremities occurring even at rest.

Many patients with LEAD may deny the specific symptomology of claudication, but tend to walk very slowly even on a straight level. Limb ischemia can be significant as evidenced by physical findings of diminished pulses, atrophic skin changes, elevation blanching, dependent rubor, and delayed venous filling time. Yet, it can be painless, a condition pathophysiologically analogous to silent myocardial ischemia. Silent limb ischemia and silent myocardial ischemia can frequently co-exist with a higher prevalence in elderly men and women.

In 1962, the widely used WHO/Rose questionnaire (Table 1) on intermittent claudication was developed for use in epidemiological surveys. However, several population studies have shown that it is only moderately sensitive (60 to 68%), although highly specific (90 to 100%). Reasons for the moderate if not poor sensitivity and high specificity were determined following its application to 586 claudicants and to 61 subjects with other causes of leg pain. The results showed two important findings: (1) over half of the false negatives were produced by one question alone, and (2) only three questions were required to maintain the specificity of the questionnaire. This knowledge, in conjunction with the pretesting of additional questions, enabled a new questionnaire to be constructed, the Edinburgh Claudication Questionnaire (Table 2). This questionnaire was tested on 300 subjects aged over 55 years attending their general practitioner, and found to be 91.3% (95% CI 88.1 to 94.5%) sensitive and 99.3% (95% CI 98.9 to 100%) specific in comparison to the diagnosis of intermittent claudication made by a physician. The repeatability of the questionnaire after six months was excellent ($\kappa = 0.76, p < 0.001$) (18).

The physician taking the history should bear in mind, as he unravels his detective work, the various risk factors and disease entities that predispose to or aggravate LEAD. Common risk factors for peripheral arterial disease are cigaret smoking, diabetes mellitus, hypertension, hyperlipidemia (particularly hypertilylyceridemia), aging, sedentary life, and obesity. Less commonly one may detect a history of gout (with hyperuricemia), homocysteinemia high sensitivity C-reactive protein, and thrombophilic states as predisposing factors for claudication. A hypertensive patient, who has none of the mentioned risk factors and complains of claudication, may have an abdominal aortic aneurysm (16). The risk factors for LEAD have been well documented in the literature (16, 19–32). Among some less known risk factors for intermittent claudication include an elevated hematocrit (2), hostile personality (25), and a decreased forced vital capacity (28). The best single discriminator for LEAD is a decreased or absent posterior tibial pulse (33).

Table 1
The WHO/Rose Questionnaire on Intermittent Claudication

(a) Do you get a pain in either leg on walking?	1. <input type="checkbox"/> Yes	2. <input type="checkbox"/> No
(b) Does this pain ever begin when you are standing still or sitting?	1. <input type="checkbox"/> Yes	2. <input type="checkbox"/> No
(c) Do you get this pain in your calf (or calves)?	1. <input type="checkbox"/> Yes	2. <input type="checkbox"/> No
(d) Do you get it when you walk uphill or hurry?	1. <input type="checkbox"/> Yes	2. <input type="checkbox"/> No
(e) Do you get it when you walk at an ordinary pace on the level?	1. <input type="checkbox"/> Yes	2. <input type="checkbox"/> No
(f) Does the pain ever disappear while you are still walking?	1. <input type="checkbox"/> Yes	2. <input type="checkbox"/> No
(g) What do you do if you get it when you are walking?	1. Stop 2. Slow down 3. Continue at same pace	
(h) What happens to it if you stand still?	1. Usually continues more than 10 minutes 2. Usually disappears in 10 minutes or less	

Definition of positive classification requires all of the following responses: "Yes" to (a) and (d); "No" to (b) and (f); "stop" or "slow down" to (g); and "usually disappears in 10 minutes or less" to (h). Grade 1 = "no" to (e) and Grade 2 = "yes" to (e) (18).

How prevalent is intermittent claudication? Intermittent claudication is present in about 4.5% of individuals over 60 years of age, compared with 2% of patients under 60 years of age (34,35). The odds ratio for claudication in men is three times higher than in women. Diabetic patients are at five times greater risk than nondiabetic individuals. Six percent of men and 3% of women between the ages of 55–74 years have claudication (36). In the diabetic patient, peripheral arteriosclerosis is 11 to 40 times higher than in the nondiabetics (36). Diabetic men with intermittent claudication have double the risk for stroke. Congestive heart failure may be three times higher when both conditions co-exist, diabetes and claudication, compared with either alone. In LEAD gangrene among diabetic and nondiabetic patients was found to be 31% and 5%, respectively (37). In the Framingham (Massachusetts) Heart Study (28), 5209 men and women aged 35–94 years were followed for cardiovascular events. For men 35–54 years old, the prevalence of peripheral arterial disease was 7.4%; for women it was 8.2%. In the ensuing two decades, the prevalence for men was 12.5% for the sixth decade of life and 11.6% for the seventh decade, whereas for women it was 14.4% and 9.4%, respectively. In the age group 75–94 years, the prevalence decreased in men to 7.1% and 5.0% in women (28). Smoking, more than any other risk

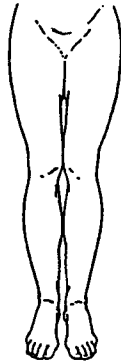
Table 2
The Edinburgh Claudication Questionnaire

- | | | |
|---|-------------------|--------------------------|
| (1) Do you get a pain or discomfort in your leg(s)? | Yes | <input type="checkbox"/> |
| | No | <input type="checkbox"/> |
| | I am able to walk | <input type="checkbox"/> |

If you answered “yes” to question (1) - please answer the following questions.
Otherwise you need not continue.

- | | | |
|--|------------------------------|-----------------------------|
| (2) Does this pain ever begin when you are standing still or sitting? | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| (3) Do you get it if you walk uphill or hurry? | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| (4) Do you get it when you walk at an ordinary pace on the level? | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| (5) What happens to it if you stan still? | | |
| Usually continues more than 10 minutes | <input type="checkbox"/> | |
| Usually disappears in 10 minutes or less | <input type="checkbox"/> | |
| (6) Where do you get this pain or discomfort? Mark the spaces(s) with “x” on the diagram below | | |

Front



Back



Definition of positive classification requires all of the following responses: “Yes” to (1), “No” to (2), “Yes” to (4). If these criteria are fulfilled, a **definite** claudicant is one who indicates pain in the calf, regardless of whether pain is also marked in other sites; a diagnosis of atypical claudication is made if pain is indicated in the thigh or buttock, in the absence of any calf pain. Subjects should not be considered to have claudication if pain is indicated in the hamstrings, feet, shins, joints, or appears to radiate, in the absence of any pain in the calf (18).

factor, can accelerate peripheral arterial disease and increase its severity (30). The physician, as in all disease entities, should expand in a detailed fashion into all of the patient’s past and present health aspects, family history, occupational history, detailed past medical history, operations, and medications.

A large percentage of claudicants (more than 65%) suffer from severe coronary artery disease, silent or symptomatic (38–42). A truly investigative approach should be taken, in order to detect in the history, or in the symptomatology or in the patient's habits, clues for coronary artery disease. A patient may have significant coronary artery disease and LEAD as well, but may not experience effort angina because claudication may stop the patient first. In a study of 25 patients (42) with intermittent claudication, eight were found to also have carotid artery obstruction. It is interesting to note here that in 1914 Ramsey Hunt termed *cerebral intermittent claudication* the brain ischemia resulting from partial carotid artery occlusion (43,44). If peripheral arterial disease co-exists with carotid disease, the probability of the same LEAD having coronary artery disease as well is 85%. Three hundred-twelve patients with LEAD were followed for 8- to 11- years (45). Sixty-nine percent died during the follow-up and 68% of the deaths were cardiac. The 5-year mortality of claudicants is 29%. In a Japanese study (46), 30% of claudicants died within 5 years and 60% of them died from cardiac or cerebrovascular disease. In claudicants, by far, the leading cause of death is cardiac.

Within 5 years from the onset of claudication, 55% of all patients will experience an improvement of their symptomatology or their symptoms will stabilize. In 14% of claudicants the ischemic process will progress. The amputation rate is 4% in 5 years. More than 80% of patients avoid ischemic complications or amputation for 5 or more years. Up to 15% of those who continue to smoke will undergo amputation within 5 years. Diabetics who smoke cigarettes have an amputation rate of about 25% within 9 years (47–49). In a landmark study by Criqui et al. (50), patients with LEAD were followed for 10 years; 62% of men and 33.3% of women died during the follow-up, as compared with 16.9% of men and 11.6% of women without peripheral arterial disease (50). Today, with our powerful therapeutic armamentarium ranging from regional thrombolysis, angiogenesis, drug eluting stents, balloon angioplasty directional and/or rotational atherectomy, and other endovascular strategies or bypass surgery, amputation should be preventable. Sadly, it is not.

CLAUDICATION IN THE ELDERLY

In the elderly, the symptoms of pain, pressure, or tightness, may be modified and more ill defined; actually they may be minimal to absent. Similarly, asymptomatic coronary heart disease with silent myocardial infarction and silent ischemia is more prevalent in the elderly. Epidemiologic studies estimate the prevalence of claudication to be as high as 10%

in patients between 65 and 70 years of age, up from 4.5% for the age group 60–64 years of age (46). The true prevalence of significant LEAD may be much higher as a result of underreporting of the specific symptomatology of claudication by the elderly. In a study of more than 500 patients older than 70 years of age, there was a much higher prevalence of intermittent claudication than in younger patients (48). The evaluation of the elderly for LEAD should rely more on meticulous physical examination and other objective data and less on the patient's complaints. Peripheral and coronary artery disease can co-exist more frequently and more silently in the elderly. The physician is challenged to identify patients at risk for gangrene, which is more prevalent in older patients, even though ischemic symptoms may be unimpressive or lacking. A detailed physical examination of the cardiovascular system in order to detect signs of peripheral ischemia should be an integral part of the physical examination of individuals over the age of 60 years. Today's medicine, in addition to an ever improving transcatheter therapeutic technologies, possesses risk factor modification methods to render gangrene and amputation preventable. Gangrene and amputation should be considered as a defeat for the physician(s) who have cared for the patient. The number of amputations should start declining in patients with LEAD. This has been the trend for the number of myocardial infarctions annually in the United States, downward for the past three decades, mainly as a result of aggressive risk factors modification and other therapeutic interventions.

Claudication is a clinical, easy to make diagnosis. Claudication of the upper extremities, although much less frequent than that of the lower extremities, is also a clinical diagnosis. The extremities should be examined carefully. Examination of the peripheral arterial system should include an evaluation of the volume and character of the arterial pulses of the carotids and of the arteries of the upper extremities: the subclavian, the brachial, the radial, and the ulnar. Physical examination should definitely encompass the abdominal aorta for abnormal pulsations, ectasias and/or bruits, and the arteries of the lower extremities: femoral, popliteal, dorsalis pedis, and posterior tibialis. The pulse volume can be graded on a scale of 0 to 4. In addition to palpation, physical examination of the peripheral arterial system should include auscultation over the carotids, auscultation over the subclavian arteries above, and below the mid-clavicular area. A bruit over the subclavian artery and disappearance of the radial pulse with compression of the subclavian artery is evidence for subclavian syndrome. On occasion, a bruit may be heard by auscultation deep in the axilla. The bruit, a composite of low frequency sounds, is better appreciated when the examiner is using the bell of the stethoscope.

Auscultation for abdominal and femoral bruits is a must in evaluating any patient.

The clinician should grade the pallor and check for elevation blanching by raising the lower extremity 30–40 degrees above the horizontal level. The examiner should press with his or her index finger to occlude capillary inflow and then, time in seconds, the return of color. Color return time of 15–20 seconds indicates moderate ischemia (50). In severe ischemia, it takes more than 40 seconds for the baseline color to return. The venous filling time (in seconds) is another useful bedside index and should be measured. Elevation and dependency tests give a rough but reliable estimate of the degree of ischemia of the lower extremities. If more objective data are desired the systolic blood pressure index can be determined (51). Ankle-to-arm systolic pressure ratios below 0.97 and 0.90 were found to be a highly probable sign of LEAD (51). The fall in ankle systolic pressure after exercise may serve as an objective indicator of the severity of hemodynamically important LEAD. This simple evaluation can become a standard test; a fall in the leg pressure that occurs after 1 minute of walk at a speed of 4 mph at 10% elevation (52) indicates hemodynamically significant LEAD. In a study of 150 patients with peripheral arterial disease and claudication the ankle mean pressure was 58 mmHg; in patients with rest pain it was 33 mmHg and in patients with chronic ulceration, it was 20 mmHg (53,54).

With electromagnetic flowmetry and Doppler ultrasound (55) it is possible to confirm and quantitate patient complaints, follow the disease progression, and document improvement following pharmacotherapy, exercise therapy, percutaneous endovascular interventions or arterial reconstructive interventions. Limb scintigraphy with thallium-201 presents advantages and great potential for clinical applications (56).

Peripheral arterial occlusion can be the initial manifestation of cardiac or systemic disease. At times, patients with chronic stable claudication may experience abrupt shortening of the distance at which claudication occurs, and this may be the only symptomatic evidence of an acute arterial occlusion either by embolization or by thrombus formation on a pre-existing arterial stenosis. The situation is not chronic and stable any more, but acute and unstable. As ischemia becomes more severe, the patient with chronic peripheral arterial disease develops ischemic pain at rest. The pathophysiologic mechanisms and the clinical presentation parallel the evolution of chronic stable angina pectoris to unstable angina and acute coronary syndromes.

When limb ischemia becomes more severe, rest pain appears usually in the toes or the foot and can become *nocturnal*. The patient with rest pain at night finds some relief by sitting up on the side of the bed with

the feet in a dependent position. A reverse Trendelenburg position can be helpful. Ischemic ulceration, usually but not always, a result of trauma to the ischemic limb can be a cause of severe pain. The ischemic ulcer has a discrete edge covered with eschar and its base is pale.

In the young, two congenital lesions are noteworthy: (1) entrapment of the popliteal artery, causing calf claudication with walking but not with running, and (2) adventitial cystic disease of the popliteal or femoral arteries (62–65). Both warrant surgical repair.

DIFFERENTIAL DIAGNOSIS

Epidemiologically, claudication caused by peripheral arterial disease affects primarily patients over the age of 40 years. Buerger's disease or thromboangitis obliterans is primarily a disease of younger men. It was first described by Leo Buerger in 1908 (57–59). Most patients with Buerger's disease are smokers. Smokers may present with peripheral vasospasm, cold fingers and toes. Cyanosis can be observed upon exposure to cold. Smokers, both men and women, (61) with peripheral vasospasm (Raynaud's phenomenon) frequently have coronary spasm with chest pain or other angina equivalent symptoms at rest, particularly in the morning hours. When observed in a hospital setting, an electrocardiogram (ECG) should be taken during chest pain; the ECG may show ST elevation and much less frequently ST segment depression. The ECG is normal between the attacks of coronary spasm. Men with Buerger's disease may also have a history of phlebitis, usually superficial. They typically seek medical attention for claudication of the arch or the calf. Physical examination is remarkable for diminished pulses of the small arteries. Frequently, the upper extremity is also involved. The etiology of Buerger's disease may relate to an autoimmune process (58,60) rather than atherosclerosis.

The differential diagnosis of claudication should also include occupational diseases with recurrent blunt trauma. Claudication can be iatrogenic in etiology, particularly among patients who suffer from migraine attacks and consume high doses of ergot containing preparations. Ergotamine derivatives can cause coronary spasm, peripheral vasospasm, and claudication (4). Arteritis associated with collagen vascular disorders, temporal arteritis (4), and Takayasu's disease (70,71) can also be causes of claudication. Infrequently, claudication can be the presenting symptom of congenital arterial narrowing or of fibromuscular hyperplasia (4). Popliteal artery aneurysm, almost always related to atherosclerosis, is another surgical disease that causes claudication, rest pain, skin ischemia, and gangrene. Ultrasonography is the most useful

diagnostic tool (66) for popliteal aneurysm. Thoracic outlet compression may be symptomatic or may present with intermittent ischemic symptoms of the arm and forearm, peripheral vasospasm and at times severe ischemia of the hand and of the fingers depending on the site of the arterial occlusion (67–69). The cause of the distal ischemia in the thoracic outlet syndrome is distal embolization from compression of the subclavian artery. Anatomically, the thoracic outlet syndrome is caused by compression of the subclavian artery by a cervical rib or by an abnormal first rib that can be palpated in the supraclavicular fossa.

Occlusive arterial disease of the upper extremity, a rare entity, can cause arm claudication and may be associated with other ischemic symptoms. Ischemia of the upper extremity should be of particular interest to the cardiologist in view of the increasing utilization of the internal mammary arteries as coronary arterial grafts.

PSEUDOCLAUDICATION

Approximately half a century after Charcot described ischemic pain in the lower extremities, Dejerine in 1911 described a syndrome he called *intermittent claudication of the spinal cord* (72–74). This neurogenic intermittent claudication is known as pseudoclaudication. In 1954, Verbiest reported in detail symptoms caused by the developmental narrowing of the lumbar vertebral canal (72). Later, a number of cases of neurospinal compression were reported (73–75). Pseudoclaudication or neurogenic claudication is bilateral or unilateral and consists of discomfort or pain in the buttocks, thighs, legs, and calves precipitated by walking uphill, on a straight level, or worse by walking downhill. Standing can also cause symptoms in neurogenic claudication. The discomfort or weakness or frank pain is relieved by sitting or by lying down (76). Bending forward or adopting a flexed position can alleviate the symptoms of neurogenic claudication (75). Leaning against a wall or bending forward can also improve the symptoms of pseudoclaudication. Prolonged standing has been associated with severe discomfort in neurogenic claudication, but not in vascular claudication. Walking downhill can precipitate pain in neurogenic claudication, but not in vascular claudication (77). In advanced cases of neurogenic claudication there is pain both in the standing and in the supine positions. Physical examination of the peripheral pulses is usually normal. By contrast in vascular claudication, the peripheral pulses are diminished or absent, there are bruits and physical findings of peripheral ischemia. The electromyogram is abnormal in neurogenic claudication and normal in vascular claudication. Patients with neurogenic claudication often complain of leg weak-

ness and may actually fall down (76). This weakness is best evoked by attempts to walk on the heels or on the toes. Any position that tends to cause the canal to become narrower will aggravate pseudoclaudication. Bending forward opens up the canal and relieves the symptoms (76,77). A lordotic position hyperextends the spine and produces radicular pain. Probably the best finding on physical examination is to provoke the symptoms by having the patient stand up or walk for a few minutes and notice if they adopt a flexed position. Standing up for several minutes will cause the patient to bend forward and lean on the nearest back support. Continued walking for several minutes induces leg distress. In about 43% of patients with neurogenic claudication, the deep tendon reflexes are reduced at the ankle level and in 18% of patients there is a reduction at the knee level. In neurogenic claudication rechecking the deep tendon reflexes of the lower extremities after walking for several minutes or standing for several minutes will show a reduction as compared with sitting (76).

Neurogenic claudication and vascular claudication are not mutually exclusive and can co-exist in about 9% of patients with either diagnosis. Vascular changes in the lower extremities may co-exist, because of the older age group in which vascular and neurogenic claudication occur. In one study (72), up to 42% of patients with pseudoclaudication were found to have absent pedal pulses. The etiology of neurogenic claudication is lumbar stenosis (78,79). In the nineteenth century, medical reports were published describing a narrow spinal canal syndrome in achondroplastic dwarfs. Other rare congenital causes of pseudoclaudication are Morquio's syndrome dysplasia, hypochondroplasia, and Down's syndrome. Apart from discogenic disease acquired causes are Paget's disease, systemic amyloidosis (80), hypertrophied ligamentum flavum, and calcium pyrophosphate crystal deposition (81). Syphilitic arteritis of the cord (Dejerius syndrome) in years past and the Foix Alajouanine syndrome are two very rare causes of neurogenic intermittent claudication (90). Degenerative joint and ligament hypertrophy is the leading cause of lumbar stenosis. The ligamentum flavum which normally does not exceed 4 mm in thickness may measure 7–8 mm. Spinal stenosis, which is the anatomic cause of neurogenic claudication, can be either congenital with a congenitally narrow spinal canal or more frequently acquired. The diameter of the canal is narrowed by the hypertrophic skeletal changes. In the middle-aged or the elderly patient who can have both neurogenic and vascular complications, the correct diagnosis, because of the variance in the presenting symptomatology and physical signs, has to be confirmed by basic laboratory evaluation. The plain radiographs of

the lumbar spine show dense bony structures and the presence of degenerative disease. Further evaluation consists of co-axial tomography and preferably magnetic resonance imaging (MRI) (82,83). Myelography is an important test (82), but is less frequently indicated even when laminectomy is being considered by the consulting surgeon. Computed tomography and MRI are complementary tests for the preoperative evaluation (82,83). Plain X-ray films are of far less value in evaluating the lumbar spine; they are more useful for the cervical spine. Pseudoclaudication, which was not widely appreciated in the past (84,85), is now part of the differential diagnosis of intermittent claudication.

Wilson (87) divided patients with this condition into two groups: (1) In the larger group, symptoms occurred during any activity or position involving extension of the lumbar spine that he termed *postural cauda equina claudication*, and (2) a smaller group of patients, with symptoms of the affected extremities after exercise that he described as *ischemic cauda equine claudication*.

According to Blau et al. (88,89), the vascular factor is more important. In exercised animals, vessels inside the canal are dilated and if the canal is narrow increased blood supply is prevented, thus leading to ischemia of the cord and the nerve roots. However, this explanation is not shared by others (90). It does not explain why neurogenic claudication occurs in the lordotic position at rest. Pseudoclaudication can be caused by other orthopedic conditions of the hips, knees, and other joints.

VASOSPASTIC CLAUDICATION

Vasospasm occurring in the digital circulation is also known as Raynaud's phenomenon. Raynaud's phenomenon is caused by abnormal vascular reactivity precipitated by exposure to cold or by emotional stress. Peripheral vasospasm was first described by the French clinician, Maurice Raynaud in 1862 (91). Usually in peripheral vasospasm there are three phases: first, the main arterial branches of the digits constrict causing a marked reduction of the blood flow to the tissues; the skin of the digits becomes pale and the patient complains of numbness, pain or paresthesias. The second phase is the cyanotic phase; the digits appear blue, purple or even black in extreme cases. The cyanotic phase continues until the blood flow is re-established as the arterial branches open up again. The cyanotic color is caused by deoxygenated hemoglobin in the post arteriolar capillaries. The third and final phase, is the post-ischemic hyperemia; the increased blood flow to the skin gives a blushed coloration. Many years ago, Allen and Brown (92) described the minimal requisites for the diagnosis of Raynaud's disease or syndrome.

It should be noted that several patients do not exhibit the classical color changes. They may complain only of cold and numb fingers or toes; thumbs are usually spared.

As with claudication caused by atherosclerosis, Raynaud's phenomenon is a clinical diagnosis. No practical laboratory test exists to diagnose peripheral vasospasm. The physician should elicit the symptoms by taking a detailed history. Color charts can also be used. The patient is asked to identify the color of the skin during a typical episode by choosing colors from actual photographs of Raynaud's attacks. Patients with peripheral vasospasm are classified as having primary or secondary Raynaud's phenomenon. In primary Raynaud's phenomenon, the patient has symmetrical attacks in the absence of digital pitting, ulceration, or gangrene. The nailfold capillaries are normal and screening tests for connective tissue disease, like erythrocyte sedimentation rate, anti-nuclear antibodies, immunoglobulin electrophoresis, etc. are normal. The prognosis of primary vasospasm is usually benign, provided the appropriate protective measures from direct exposure to cold are taken. The situation is different in secondary Raynaud's phenomenon. The most common cause of secondary Raynaud's phenomenon is an underlying collagen vascular disease. Several conditions are associated with Raynaud's (91-97). CREST consists of Calcinosis, Raynaud's phenomenon, Esophageal changes, Sclerodactyly, and Telangiectasias. Raynaud's phenomenon may precede a connective tissue disorder for years (94). The prognosis in secondary Raynaud's phenomenon depends on the underlying connective tissue disease. The most common cause of secondary Raynaud's phenomenon is scleroderma. Approximately 90% of patients with scleroderma have Raynaud's phenomenon and it can be the first clinical expression of the disease. Peripheral vasospasm has also been associated with systemic lupus erythematosus in about 30 to 40% of patients. Approximately 20% of patients with dermatomyositis describe Raynaud's phenomenon. An association of Raynaud's phenomenon with Sjogren's syndrome has been described. The existence of Raynaud's phenomenon in collagen vascular diseases may adversely influence their prognosis. In lupus erythematosus, for example, the presence of Raynaud's symptomatology has been associated with pulmonary hypertension. Any kind of vasculitis or vascular injury can be subsequently associated with Raynaud's phenomenon. Raynaud's symptoms in patients with giant cell arteritis (polyarteritis nodosa) can evolve to cutaneous gangrene (93-96).

Hyperviscosity states like cryoglobulinemia have been associated with Raynaud's phenomenon: from reversible vasospasm to frank pur-

pura. Certain pharmacologic agents can cause or aggravate Raynaud's phenomenon. The most notorious for that toxicant is nicotine. Smoking can cause both coronary and peripheral vasoconstriction and has been associated with coronary spasm in men and women (61). Cocaine is another cause of both coronary and peripheral vasospasm. Ergotamine derivatives can also produce both coronary and peripheral vasospasm. Raynaud's phenomenon occurs in about 30% of cases following chemotherapy with Vinca alkaloids and bleomycin. β -Blockers have also been reported to cause Raynaud's phenomenon, but very rarely as have certain sympathomimetic agents used as over-the-counter cold preparations.

The pathophysiology of peripheral vasospasm is unclear. The author of this chapter would like to propose the hypothesis that it is a result of endothelial dysfunction. In the late 1920s, Sir Thomas Lewis hypothesized that Raynaud's disease is a result of a *local vascular fault* (99), but after all these years, the *fault* has not been adequately defined. An attractive hypothesis is an imbalance of the endothelial function, involving endothelin (100–106). Endothelin (107) that is produced by the endothelial cells is a potent vasoconstrictor, whereas nitric oxide, an endothelium-derived relaxing factor (EDRF), is a potent vasodilator (104). Prostacycline and prostaglandins also produced by the endothelial cells normally counteract thromboxane, which is a potent platelet derived-vasoconstrictor. A parallel mechanism leading to peripheral vasospasm can be increased sensitivity to α -adenoceptor agonists (102).

Individuals with primary Raynaud's phenomenon are more likely to respond well to therapy than individuals with secondary Raynaud's phenomenon. Many patients with mild Raynaud's phenomenon are minimally disabled, but often frightened by the cutaneous color changes. The majority of patients do not need pharmacologic intervention. Protection of the upper and lower extremities from direct exposure to cold is a practical approach. Although Raynaud's phenomenon is more severe during the winter, recurrent attacks do occur in any season upon a sudden cold stimulus. Often a rapidly changing temperature is more likely to precipitate peripheral vasospasm than exposure to a lower, but constant temperature. A central body chill is as likely to provoke an attack of Raynaud's as is a direct cold exposure to the hands. In a number of patients, emotional stress is a major precipitating factor. All known aggravating factors should be avoided and by all means smoking. Ketanserin has been tried in the treatment of Raynaud's phenomenon occurring with scleroderma (109).

Calcium channel blockers (CCBs) are the most widely used pharmacologic agents for the treatment of peripheral vasospasm (110–112). Sympatholytic agents have also been used in the treatment of Raynaud's phenomenon. Topical nitroglycerin ointment can be applied with a nocturnal nitrate-free interval to avoid nitrate tolerance.

The treatment of claudication due to LEAD is multifaceted: aggressive risk factor modification, regression therapy of the atheromas, pharmacotherapy, exercise therapy, endovascular transcatheter therapeutic interventions, angiogenesis, and vascular graft procedures.

In any patient with documented LEAD, risk assessment for cerebrovascular, and coronary heart disease of utmost importance.

REFERENCES

1. Walker RT, Woodyer AB, Dormandy JA. Venous claudication. A report of 15 cases and a review of the literature. *Int Angiol* 1985; 4:365–367.
2. Kontos HA. Arteriosclerosis obliterans. Cecil Textbook of Medicine, 20th ed. Bennett/Plum, 1996, pp. 350–351.
3. Anstrom SM, El-Hayek A, Comianos M, Tamulouis DJ. Mitral valve disease associated with long-term ergotamine use. *Southern Med J* 1993;86:1179–1181.
4. Ouriel K, Green RM. Arterial disease. In: Schwartz S, ed. Principles of Surgery, 7th ed. New York:McGraw-Hill Health Professions Division, 1999, p. 981.
5. Waal Manning HJ. Hypertension: which beta-blocker? *Drugs* 1976; 12:412–441.
6. Radack K, Deck C. β -adrenergic blocker therapy does not worsen intermittent claudication in subjects with peripheral arterial disease. *Arch Int Med* 1991; 151:1769–1776.
7. Lepautelo M. Beta-blockade and intermittent claudication. *Acta Med Scand* 1985; 700:S1–S48.
8. Friedman SA, Pandya M, Grief E. Peripheral arterial occlusion in patients with acute coronary heart disease. *Am Ht J* 1973; 86:415.
9. Barnhorst DA, Barner HB. Prevalence of congenitally absent pedal pulses. *N Engl J Med* 1968; 278:264.
10. Stephens G. Palpable dorsalis pedis and posterior tibial pulses. *Arch Surg* 1962; 84:662.
11. Friedman SA. Prevalence of palpable wrist pulses. *Br Ht J* 1970; 32:316.
12. Juergens JL, Barker NW, Itines EA. Review of 520 cases with special reference to pathogenic and prognostic factors. *Circulation* 1960; 21:188–195.
13. Arnold AM. Chest pain in a patient with congenital heart disease. *Cleveland Cl J Med* 1995; 62:206–208.
14. Wynne J. Miscellaneous conditions of the heart: tumor, trauma and systemic disease. In: Cecil Textbook of Medicine, 20th ed. Bennett/ Plum, 1996, pp. 357–359.
15. Hinton RC, Kistler JP, Callan JT, et al. Influence of etiology of atrialfibrillation a incidence of systemic embolism. *Am J Cardiology* 1977; 40:509.
16. Lord JW Jr, Rossi G, Daliana M, Drago JR, Schwartz M. Unsuspected aneurysm as a cause of peripheral arterial occlusive disease. *Am Surg* 1973; 177:767–771.
17. Hans SS, Zesking HJ. Routine use of limited abdominal aortography with digital subtraction cardiac and cerebral angiography. *Stroke* 1995; 26:1221–1224.
18. Leng GC, Fowkes FGR. The Edinburgh Claudication Questionnaire: an improved version of the WHO/Rose Questionnaire for use in epidemiological surveys. *J Clin Epidemiol* 1992; 45:1101–1109.

19. Lepautello M, Lassila R. Smoking and occlusive peripheral arterial disease. Clinical review. *Eur J Surg* 1991; 157:83–87.
20. Hratt WR, Regeustainer JG, Hargarten ME, Wollel EE, Brass EP. Benefit of exercise conditioning for patients with peripheral arterial disease. *Circulation* 1990; 81:602–609.
21. Lowe GD, SaniaPadi A, Turner A, Lieberman P, Pollock J, Drury J. Strides on hematocrit in peripheral arterial disease. *Klin Wochenschr* 1986; 64:969–976.
22. Siitonen O, Vusitupa M, Pyorala K, Voutilainen E, Lansimies E. Peripheral arterial disease and its relationship to cardiovascular risk factors and coronary artery disease in newly diagnosed non-insulin dependent diabetes mellitus. *Acta Med Scand* 1986; 220:205–212.
23. Radack K, Wyderski RJ. Conservative management of intermittent claudication. *Ann Intern Med* 1990; 113:135–146.
24. Balkau B, Vray M, Eschewege E. Epidemiology of peripheral arterial disease (Review). *J Cardiovasc Pharmacol* 1994; 23:S8–S16.
25. Deary IJ, Fowkes FG, Dannan PT, Housley E. Hostile personality and risk of arterial disease in the general population. *Psychosis Med* 1994; 56:197–202.
26. Brand FN, Abbott RD, Kannel WB. Diabetes, intermittent claudication and risk of cardiovascular events. The Framingham Study. *Diabetes* 1989;38:504–509.
27. Pomrehn P, Duncan B, Weissfeld L, Wallace RB, Barnes R, Heiss G, et al. The association of dyslipoproteinemias with symptoms and signs of peripheral arterial disease. The Lipid Research Clinics Program Prevalence Study. *Circulation* 1986; 73:1100–1107.
28. Kannel WB, McGee DL. Update on some epidemiologic features of intermittent claudication. The Framingham Study. *J Am Geriatr Soc* 1985; 33:13–18.
29. Horby J, Grande P, Vestergaard A, Grauhoft AM. High-density lipoprotein cholesterol and arteriography in intermittent claudication. *Eur J Vasc Surg* 1989; 3: 333–337.
30. Myers KA. Relationship of smoking to peripheral arterial disease. *Australian Family Physician* 1979; 8: 765–768.
31. Lowe GD, Fowkes FG, Dawes J, Donnan PT, Lennie SE, Housley E. Blood viscosity, fibrinogen and activation of coagulation and leucocyte in peripheral arterial disease and the normal population in the Edinburgh Artery Study. *Circulation* 1993; 87:1915–1920.
32. Gagnan F, Dagenais GR, Robitaille NM, Lupien PJ. Impact of systolic and diastolic blood pressure on ischemic vascular diseases in French-Canadian men from 1974 to 1990. *Can J Cardiol* 1994; 10:97–105.
33. Criqui MH, Frouek A, Klauber MR, Barrett-Connor E, Gabriel S. The sensitivity, specificity and predictive value of traditional clinical evaluation of peripheral arterial disease: results for non-invasive testing in a defined population. *Circulation* 1985; 71:516–522.
34. McDaniel MD, Cronnerwett JL. Basic data related to the natural history of intermittent claudication. *Ann Vasc Surg* 1989; 3:273–277.
35. Fowkes FG, Housley E, Cawood EH, Macintyre CC, Ruckley CV, Prescott RJ. Edinburgh Artery Study: Prevalence of asymptomatic and symptomatic peripheral arterial disease in the general population. *Int J Epidemiol* 1991; 20:384–392.
36. Mahmoud AH. A population sample study of peripheral occlusive arterial disease. Thesis, Univ. of Michigan, Ann Arbor, Michigan, 1964.
37. Jonason T, Ringquist I. Diabetes mellitus and intermittent claudication. Relation between peripheral vascular complications and location of occlusive atherosclerosis of the legs. *Acta Med Scand* 1985; 218:217–221.

38. Caralis DG. Assessing perioperative cardiac risk in peripheral arterial diseases. Balas's har. *Hell Vasc Surg Soc Athens*, 1993;1:21-27.
39. Hertzner NB, Beven EG, Young JR, et al. Coronary artery disease in peripheral vascular patients. A classification of 1000 coronary angiograms and results of surgical management. *Ann Sur* 1984; 199:223.
40. Mautner GC, Maunter SL, Roberts WC. Amounts of coronary arterial narrowing by atherosclerotic plaque at necropsy in patients with lower extremity amputation. *Am J Cardiol* 1992; 70:1147.
41. Mautner GC, Berezowski K, Mautner SL, Robert WC. Degrees of coronary arterial narrowing at necropsy in with large fusiformis abdominal aortic aneurysms. *Am J Cardiology* 1992; 70:1143.
42. Stevenow L, Karlsson S, Lilia B, Lindgarde F. High prevalence of coronary heart disease in patients with intermittent claudication. *Acta Chir Scand* 1988; 154: 447-451.
43. Hunt JR. The role of the carotid arteries in the causation of vascular lesions of the brain, with remarks on certain special features of the symptomatology. *Am J Med Sci* 1914; 147:704.
44. Dean RH. Carotid artery occlusive disease. In: Sabiston, Textbook of Surgery, 14th ed. Philadelphia:W.B. Saunders, 1991, pp. 1580-1583.
45. Lassila R, Lepantelo M, Lindfors O. Peripheral arterial disease. Natural outcome. *Acta Med Scand* 1986; 220:295-301.
46. Ohta T, Kato T, Kazui H, Koudo M, Tsuchioka H, Shionoya S. The prognosis of intermittent claudication. (*Jap*) *Nippon Geka Gakka Zasshi* 1989;90:615-621.
47. Juergens JL, Barker NW, Hines CA. Arteriosclerosis obliterans review of 520 cases with special reference to pathogenic and prognostic factors. *Circulation* 1960; 21:188-195.
48. Imperato AM, Kiu GE, Davidson T, Crowley JG. Intermittent claudication. Its natural course. *Surgery* 1975; 78:795-799.
49. Schadt DC, Hines EA Jr, Juergens JL, Barker NW. Chronic atherosclerotic occlusion of the femoral artery. *J Angio* 1961; 175:937-940.
50. Criqui MH, Langer RD, Frouck A, Feigelson HS, Klauber MR, McCann TJ, Browner D. Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med* 1992; 326:301-306.
51. Spittell JA Jr. Occlusive peripheral arterial disease. Guidelines for office management. *Postgrad Med* 1982; 71:137-142,146,150-151.
52. Postiglione A, Cicerano V, Gallotta G, Chasso A, Lamenza F, Rubba P, Manciu M. Prevalence of peripheral arterial disease and related risk factors in elderly institutionalized subjects. *Gerontology* 1992; 38:330-337.
53. Laing SP, Greenhalgh RM. Standard exercise test to assess peripheral arterial disease. *Br Med J* 1980; 280:13-16.
54. Belcaro G, Sager P, Borgwardt A, Holm A, Jelnes R, Rosenkvist L, Possati F. Arterial pressure measurements correlated to symptoms and signs of peripheral arterial disease. *Acta Chir Belgrca* 1983;83: 320-326.
55. Lee BY, Trainor FS, Thoden WR, Kavner D, Madden JL. Use of non-invasive electromagnetic flowmetry in the assessment of peripheral arterial disease. *Surg Gynecol Obst* 1980; 150:342-346.
56. Seder JS, Botvinich EM, Rahimtooda SH, Goldstone J. Price DC. Detecting and localizing peripheral arterial disease: assessment of (201)Tl scintigraphy. *AJR Am J Roentgenol* 1981;137:373-380.
57. Lie JT. Thromboangiitis obliterans (Buerger's disease) revisited. *Pathol Annu* 1988; 23:257.

58. Wheeler HB. Thromboangiitis obliterans (Buerger's disease). In: Sabiston, Textbook of Surgery, 14th ed. Townsend CM, ed. Philadelphia:W.B. Saunders, 1991, pp. 1637–1640.
59. McKusick VA, Harris WS, Ottesea OE, et al. Buerger's disease. A distinct clinical and pathologic entity. *JAMA* 1962;181–185.
60. Adar R, PapaMZ, Halpern Z, et al. Cellular sensitivity to collagen in thromboangitis obliterans. *N Engl J Med* 1983; 308:1113.
61. Caralis DG, et al. Smoking is a risk factor for coronary spasm in premenopausal women. *Circulation* 1992;85:905–909.
62. Collis PS, Mc Donald PT, Lim RC. Popliteal artery entrapment: an evolving syndrome. *J Vasc Surg* 1989; 10:484–490.
63. Barnett AJ, Dugdale L, Fergresan I. Disappearing pulse syndrome due to myxomatous degeneration of the popliteal artery. *Med J Austral* 1966; 2:355–358.
64. DeWeese JA. Pedal pulses disappearing with exercise. *N Engl J Med* 1960;262: 1214–1217.
65. Ishikawa K. Cystic adventitial disease of the popliteal artery and of other stem vessels in the extremities. *Jpr J Surg* 1987; 17:221–229.
66. Seddan AM. Popliteal artery aneurysms. *Postgrad Med* 1993; 94:125–128.
67. Dale WA. Thoracic outlet compression syndrome; critique. *Arch Surg* 1982; 117:1437.
68. Harding A, Silver D. Thoracic outlet syndrome. In: Sabiston, Textbook of Surgery, 14th ed. Townsend CM, ed. Philadelphia:W.B. Saunders, 1991, pp. 1757–1761.
69. Parachuri R, Adaues EM. Entrapment neuropathies. *Postgrad Med* 1993; 94: 39–51. (Thoracic outlet syndrome in p. 45.)
70. Takayasu M. Case of queer changes in central blood vessels of the retina. *Acta Soc Optham Jap* 1908; 12:2554.
71. Ishikawa K. Natural history and classification of occlusive thomboartopathy (Takayasui's disease). *Circulation* 1978; 57:27.
72. Snyder EN Jr, Mulfinoer GL, Lambert RW. Claudication caused by compression of the cauda equine. *Am J Surg* 1975; 130:172.
73. Goodreau JJ, Creasy JK, Flanigan DP, Burnham SF, Kudina JC, Schafter MF, et al. Rational approach to the differentiation of vascular and neurogenic claudication. *Surgery* 1978; 84:749–757.
74. Evans JG. Neurogenic intermittent claudication. *Br Med J* 1964; 2:985.
75. Wilson CB, Ebni G, Grollnus J. Neurogenic intermittent claudication. *Cl Neurosurg* 1971; 18:62.
76. Karayannakos PE, Yahoo D, Vasco JS. Narrow lumbar spinal canal with "vascular" syndromes. *Arch Surg* 1976; 111:803.
77. Karanaugh GJ, Svein HJ, Holman CB, Johnson RM. Pseudoclaudication syndrome produced by compression of the cauda equine. *JAMA* 1968; 206:2477–2481.
78. Malis LI. Lumbar stenosis. *Mt Sin J Med* 1991; 58:121–124.
79. Gaskill MF, Lukin R, Wiot JC. Lumbar spine disease and stenosis. *Radiol Cl North Am* 1991; 29:753–764.
80. Harats N, et al. Spinal claudication in systemic amyloidosis. *J Rheumatol* 1989; 16:1003–1006.
81. Drouillard PJ, et al. Lumbar spinal ateliosis associated with hypertrophied ligamentum flavum and calcium pyrophosphate crystal deposition. *Am Osepopath Assoc* 1988; 88: 1019–1021.
82. Sutton D, ed. A Textbook of Radiology and Imaging. 4th ed. New York:Edinburgh 1987.
83. Hammerschlag SB, Wolpert SM, Carter BL. Computed tomography of the spinal cord. *Radiology* 1976; 121:361.
84. Wipf JE, Deyo RA. Low back pain. *Med Cl North Am* 1995; 79:231–246.

85. Hines EA. Some types of distress in the lower extremities simulating peripheral vascular disease. *Med Cl North Am* 1958; 42:991–996.
86. Brish A, Lerner MK, Braham J. Intermittent' claudication from compression of the cauda equina by a narrowed spinal canal. *J Neurosurg* 1964; 21:207–211.
87. Wilson CB. Significance of the small lumbar spinal canal. Cauda equina compression syndromes due to spondylosis. *J Neurosurg* 1969; 31:499–506.
88. Blau JN, Logue V. Intermittent claudication of the cauda equina. *Lancet* 1961; 1:1081–1086.
89. Blau JN, Rushworth G. Observations in the blood vessels of the spinal cord and their responses to motor activity. *Brain* 1958; 81:354–363.
90. Cooke TD, Lehmann PO. Intermittent claudication of neurogenic origin. *Can. J Surg* 1968; 11:151–159.
91. Raynaud M. On local asphyxia and symmetrical changes of the extremities. Selected monograph. London. New Sydenham Society, 1888.
92. Allen EV, Brown EG. Raynaud's disease. A critical review of minimal requisites for diagnosis. *Am J Med Sci* 1932; 183:187–200.
93. de Takats G, Fowler EF. Raynaud's phenomenon. *JAMA* 1962; 179:88–106.
94. Blunt RJ, Porter JM. Raynaud's syndrome. *Semin Arthritis Rheum* 1981; 10:282.
95. Porter JM, Bardana EJ, Baur GM, Wesche DH, et al. The clinical significance of Raynaud's syndrome. *Surgery* 1976; 80:756.
96. Joyce JW. Raynaud's phenomenon. In: Hurst's the heart: arteries and veins. 8th ed., Schlant KC, Alexander RW, eds. New York: McGraw-Hill, 1994, pp. 2189–2190.
97. Porter JM, Snider RL, Bardana EJ, et al. The diagnosis and treatment Raynaud's phenomenon. *Surgery* 1975; 77:11.
98. Taylor W, Pelmeur PL. Raynaud's phenomenon of occupational origin. An epidemiological survey. *Acta Chir Scand* 1976; 465:27.
99. Kontos HA. Vascular diseases of the limbs. In: Cecil Textbook of Medicine, 20th ed. Bennet/Plum 1996, pp. 346–350.
100. Gifford RW Jr, Hines EA Jr. Raynaud's disease among women and girls. *Circulation* 1957; 16:1012.
101. Lewis T. Experiments relating to the peripheral mechanisms involved in spastic arrest of the circulation in the fingers, a variety of Raynaud's disease. *Heart* 1929; 15:7.
102. Edwards JM, Phinney ES, Taylor IM Jr, Kennan EJ, Porter JM. Alpha-2 adrenoceptor differences in vasospastic and obstructive Raynaud's syndrome. *J Vasc Surg* 1987; 5:38.
103. Marsden PA, Danthuluri NR, Brenner BM, Ballerman BJ, Brock TA. Endothelin action on vascular smooth muscle involves inositol triphosphate and calcium mobilization. *Biochem Biophys Res Commun* 1988; 158:86–93.
104. Luscher TF, Yang Z, Diederich D, Buhler FR. Endothelium-derived vasoactive substance. Potential role in hypertension, atherosclerosis and vascular occlusion. *J Cardiovasc Pharmacol* 1989; 14:563–569.
105. Vane JR, Botting R, Masaki T. Endothelin. *J Cardiovasc Pharmacol* 1989; 13: S1–S231.
106. Luscher TF, Boulanger CM, Dohi Y, Yang Z. Endothelium-derived contracting factors. *Hypertension* 1992; 19:117–130.
107. McMillen M.A., Sumpio B.E.: Endotherlins: Polyfunctional Cytokines. *J. Am. Coll. of Surgeons* 1995; 180:621–637.
108. Levin ER. Mechanisms of disease: Endotherlins. *N Engl J Med* 1995; 333: 356–363.

109. Roald OK, Sean E. Treatment of Raynaud's phenomenon with ketanserin in patients with connective tissue disorders. *Br Med J* 1984;289:577-579.
110. Kahan A, Weber S, Amor B, et al: Nifedipine and Raynaud's phenomenon (letter). *Ann Int Med* 1981; 94:546.
111. Smith DC, McKendry RJ. Controlled trial of Nifedipine in the treatment of Raynaud's phenomenon. *Lancet* 1982; 2:1299.
112. Stone PH, Autman EJ, Mueller JE. Calcium channel blocking agents in the treatment of cardiovascular disorders. Part II. Hemodynamic effects and clinical application. *Am Int Med* 1980; 93:886.

2

Noninvasive Diagnostic Evaluation of Peripheral Arterial Disease

*Nicos Labropoulos, PhD, DIC, RVT
and Apostolos K. Tassiopoulos, MD*

CONTENTS

INTRODUCTION
DIAGNOSTIC EVALUATION
REFERENCES

INTRODUCTION

The pathogenesis of arterial stenosis or occlusion may be secondary to a wide spectrum of etiologic factors including atherosclerosis, thrombosis, embolic events of various etiology, fibromuscular dysplasia, vasculitides, dissection, trauma, external compression, and vasospastic syndromes. Atherosclerosis is by far the most common cause of arterial stenosis.

Atheromatic plaques have been identified as early as the first two decades of life, but usually become hemodynamically significant after the age of 50. They can develop in most of the arteries in the body, and are most commonly located in the area of arterial bifurcations. A hemodynamically significant arterial stenosis reduces blood flow in the capillary bed distal to it. The extent of this interference is related to the severity of the stenosis and is determined by strict hemodynamic principles. Tissue perfusion distal to an arterial stenosis can be maintained by development of a network of collateral vessels around the stenosis,

From: *Clinical Hypertension and Vascular Diseases: Lower Extremity Arterial Disease*
Edited by: D. G. Caralis and G. L. Bakris © Humana Press Inc., Totowa, NJ

increase of the cardiac performance, and dilatation of the local arterioles and precapillary sphincters.

There are three levels of occlusive disease in the lower limb arteries: aortoiliac, femoropopliteal, and infrapopliteal disease. Disease confined to one level may be asymptomatic or it can present with intermittent claudication. The presence of two or three levels of disease are symptomatic, and patients usually present with severe claudication or rest pain. Three levels of disease are often seen in patients with skin damage and critical limb ischemia. Without an intervention most limbs with critical ischemia will be amputated within 1 year. In patients with diabetes mellitus the disease is usually confined in the infrapopliteal vessels. Such patients may develop critical limb ischemia with one level of disease because this is the most distal of the three. Usually, multiple stenoses and/or occlusions are found in at least two of the run-off arteries. Although it is known that atherosclerosis develops most often in bifurcations, in the lower extremities the most frequently involved site is the superficial femoral artery. Other common sites are the aortoiliac, iliac, femoral popliteal, and tibioperoneal trunk bifurcations.

DIAGNOSTIC EVALUATION

History and Physical Examination

The evaluation of a patient with lower extremity arterial occlusive disease starts with a detailed history and a complete physical examination (1). A thorough pulse exam of both upper and lower extremities is of utmost importance. Absence of palpable pulses at any level indicates hemodynamically significant lesion(s) to the main artery proximal to that level. Thus, absence of palpable femoral pulses is suggestive of severe stenosis or occlusion of the ipsilateral iliac artery (2).

Physiological Testing

Hemodynamic testing of the lower extremity includes noninvasive methods that evaluate the dynamic function of the circulation. Various techniques have been developed for noninvasive assessment including segmental pressures, ankle-brachial indices, continuous-wave Doppler waveform analysis, pulse volume recordings, transcutaneous oximetry, treadmill testing, and duplex scanning. Inexpensive equipment and a short learning curve have made hemodynamic testing widely used for the diagnosis of lower extremity arterial disease.

Systolic pressures can be taken at different locations in the lower extremities to help identify the location of arterial disease. Most commonly, pressures are taken at the high thigh, lower thigh, calf, and ankle.

A pressure gradient > 20 mmHg between cuffs is considered indicative of significant arterial disease. For example, a pressure difference of >20 mmHg between the high and low thigh cuffs indicates the presence of a hemodynamically significant superficial femoral artery stenosis. Segmental pressures can give a general idea of the location of the disease, but cannot ascertain the exact site, extent, or severity of a lesion (3).

The ankle-brachial index (ABI) is the best screening test to evaluate the presence or absence of arterial disease in the lower extremities. It is a ratio between the systolic pressure at the ankle in the arms (Fig. 1). In a person with normal arterial circulation, the ankle pressures should be equal or greater than the brachial pressures. Therefore, the normal ABI value is one or higher. Any patient with an $ABI < 0.9$ has lower extremity arterial occlusive disease. The ABI is an important tool in diagnosing and following up arterial disease (4). It is helpful in the follow-up of patients who have undergone revascularization procedures such as angioplasty or bypass grafting. Success of these procedures and progression of disease can be monitored using the ABI. For example, during follow-up of patients who underwent infrainguinal bypass grafting, a drop of >0.15 in the ABI would indicate the development of significant stenosis either in the graft or in the native arteries. In patients with calcified noncompressible arteries, the ABI is of no value because erroneously high pressures are measured in the lower limb. In these occasions a toe pressure is taken instead (1).

Continuous-wave (CW) Doppler waveforms are commonly used in conjunction with segmental pressures or ABIs. Waveforms can help in identifying the location of arterial disease in the lower extremity. Waveforms are usually taken from the common femoral, superficial femoral, popliteal, dorsalis pedis, and posterior tibial arteries and recorded on a strip chart recorder. Qualitative analysis of the waveforms is performed to identify abnormalities in the arterial circulation. The presence of triphasic waveforms at any level indicates absence of a hemodynamically significant arterial lesion proximal to that level. Attenuated waveforms that have lost their triphasic appearance indicate an arterial stenosis proximally.

Pulse volume recordings (PVRs) are similar to the waveforms obtained by CW Doppler and can be used to identify location of disease in the lower extremity. Blood pressure cuffs are placed on the high thigh, low thigh, calf, and ankle of the lower extremity. Cuff pressure changes reflect a change in cuff volume, which reflects changes in limb volume. Pulse volume recordings from each site can be recorded on a strip chart recorder. Differences in the PVR waveforms can be used to determine the location and severity of arterial disease.

Ankle Brachial Index

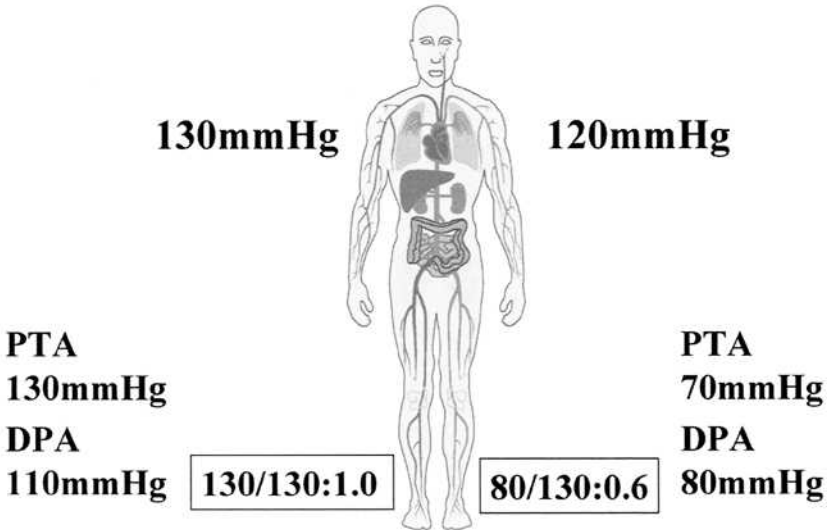


Fig. 1. The measurement of ABI involves bilateral arm pressure measurements. The highest arm pressure is used in the estimation of the ABI. Of the arteries at the ankle level the highest pressured is used.

Transcutaneous oximetry (TCPO₂) can be used in the lower extremity to evaluate the oxygen supply to the skin. This procedure is used most often in patients with severe arterial disease requiring surgical reconstruction or amputation. TCPO₂ values are obtained by placing an electrode on several areas in the lower extremity. Most commonly, values are taken at the chest (control) above the knee, below the knee, and at several areas on the foot. A measurement can also be taken on the dorsum of the foot with a 30 degree elevation. TCPO₂ values can be helpful in patients who have nondiagnostic ABIs (falsely elevated pressures as a result of calcification of vessels). Values obtained from TCPO₂ measurements can aid the surgeon in decisions regarding amputation site and healing potential.

Segmental pressures (ABIs) and CW waveforms at rest can be normal in patients with significant arterial lesions. This can be caused by collateral circulation providing adequate flow without significant reduction in pressure. CW waveforms can appear normal if the sample is taken distal to a lesion, where the flow has had a chance to normalize. By exercising a patient on a treadmill, the working muscles require increased blood flow. Symptoms and their severity can be reproduced and walking time

can be documented. In the event of a significant arterial lesion, pressures will drop after exercise. *Treadmill testing* can provide a baseline for patients who have undergone interventional or reconstructive procedures. Improvement or progression of disease can be followed with exercise testing.

Toe pressures can be taken using a photoplethysmography (PPG) probe. A small cuff (2.5 cm) is placed around the digit and the PPG probe is attached with double-stick tape to the pad. Toe pressures can be used in patients with nondiagnostic segmental pressures resulting from calcific vessels. A toe pressure >80 mmHg is normal. Pressures from 80–30 mmHg indicate mild to moderate disease and those <30 mmHg indicate critical disease.

Skin perfusion pressure measurements are taken with laser Doppler. Skin perfusion pressure is used in patients with critical limb ischemia requiring surgical reconstruction or amputation. Like the toe pressures, it is useful in patients with falsely elevated pressures caused by arterial wall calcification.

Color Flow Duplex Scanning

Duplex scanning (with or without color flow) combines a B-mode image with Doppler spectral waveform analysis. Unlike segmental pressures or continuous-wave Doppler waveforms, duplex scanning allows direct visualization of the arterial segment. Location and severity of the disease can be documented with high accuracy. Duplex scanning can also differentiate between different types of disease such as stenosis, occlusion, or thrombosis. Using velocity criteria, the degree of stenosis can be documented (5). Color flow can be helpful in identifying changes in velocity resulting from an arterial stenosis. These changes are used to calculate the severity of stenosis (5). Thus, duplex scanning provides a combination of anatomic and physiologic information that other imaging or physiologic testing modalities cannot offer.

BASIC PRINCIPLES

Inertial losses depend on the kinetic energy of the blood ($DP = K/2pv^2$). Because p is a constant changes occur only in the velocity. These changes are significant across a severe stenosis (6). According to the equation of continuity, flow (cross-sectional area \times velocity) is the same at any point along a tube segment with no branches

$$A_1V_1 = A_2V_2 \quad \text{or} \quad A_1/A_2 = V_2/V_1$$

The V_2/V_1 from the equation, where V_2 is the peak systolic velocity (PSV) at the stenotic segment and V_1 the PSV at the normal diameter

segment proximal to the stenosis, is being used to detect significant stenosis in peripheral arteries (7). This ratio is not applicable in the internal carotid artery because the carotid bulb diameter is usually 1.2 times larger than the common carotid diameter, and therefore other complex flow phenomena occur (8). This is one of the main reasons for which different laboratories have to establish their own criteria to detect carotid artery stenosis.

Blood flow in large vessels at rest is laminar with relatively uniform velocities. Narrowing or obstruction causes disruption of the laminar flow, creating vortices and whirls of different velocities and directions. This flow is called turbulent and generally characterizes flow across an area of stenosis (6).

CRITICAL STENOSIS

A stenosis is hemodynamically significant when a reduction in the blood pressure or flow is being observed. In an experimental setting it has been shown that pressure or flow decrease when a lesion produces at least 75% *area reduction*. This decrease in the luminal area corresponds to a 50% *axisymmetric diameter stenosis* (6,9–12).

The energy loss across a stenosis is inversely proportional to the fourth power of the minimal radius at the stenosis, and to the ratio of the fourth power of the radius at the prestenotic and stenotic site. It also depends on the blood flow velocity. In a low resistance high-flow artery, flow reduction occurs at a lesser degree of narrowing than in a low-flow (high resistance) artery. Therefore, the resistance of the vascular bed distal to the lesion also affects the energy loss across the stenosis. This phenomenon is well illustrated in the lower extremity arteries where at rest (*high-resistance low-flow system*) may be nonsignificant, but during exercise (*low-resistance high-flow system*) may become significant (6).

The length of the stenosis accounts for viscous energy loss as shown by the Poiseuille's equation. However, such energy loss is less significant compared to that occurring from further reduction in the vessel's diameter. The amount of resistance offered by a stenosis depends largely upon entry and exit blood flow phenomena. This explains why a 2 cm long stenosis in an artery would produce much less resistance than two separate 1 cm long stenoses with the same degree of narrowing (6).

DIAGNOSTIC CRITERIA FOR ARTERIAL STENOSIS BY DUPLEX SCANNING

Criteria for detecting significant stenosis have been developed for peripheral arteries. These criteria have been derived by correlating the ultrasound parameters to angiography, pressure measurements across the stenosis, and measurements on operative specimens. For peripheral

arteries and grafts a V2/V1 ratio >2.0 (7,13,14) indicates the presence of significant stenosis; this is the most widely recommended diagnostic criterion (Fig. 2). However, few centers are using as a cut-off value a ratio >2.5 for better specificity and a very small reduction in sensitivity. A pooled analysis using the above criteria showed that the sensitivity and specificity for detecting aortoiliac stenosis were 86%, 95% CI 80–91 and 97%, 95% CI 95–99, respectively (14). A V2/V1 ratio >5.5 and/or an end-diastolic velocity >60 cm/s indicates that the diameter reduction is $>75\%$. A DPSV (PSV difference across a stenosis) >160 cm/s at rest has shown a sensitivity of 85% and a specificity of 88% in the aortoiliac segment. After exercise a DPSV >160 cm/s has a sensitivity of 100% and a specificity of 82% (15).

The waveform pattern obtain by duplex scanning can also be used for diagnosing proximal or distal disease (16,17). A triphasic waveform in the common femoral artery indicates that the ipsilateral proximal vessels are normal. A biphasic waveform would indicate stenosis that is not significant, and a monophasic waveform would signify the presence of significant stenosis or occlusion (Fig. 3). A low-end diastolic velocity indicates a tight stenosis or occlusion distal to the measurement (Fig. 4).

Presently, there are no standards by which hemodynamic testing is used. Initially, a clinical examination is performed in an outpatient setting. Depending on the signs and symptoms of arterial insufficiency, any of the earlier discussed tests may be performed. It should be noted that in many centers, the decision to perform a noninvasive test may be linked to the type of treatment the patient will receive. For example, a physician who plans to treat a claudication patient with an angioplasty or a bypass procedure might request a duplex scan. On the other hand, a duplex scan would not be considered in a patient where no intervention is planned. The following are basic algorithms that can be helpful in deciding which method of testing is most beneficial in patients presenting with claudication and rest pain.

In a patient presenting with symptoms of an acute arterial occlusion, time is critical. If the limb is threatened on physical exam, the patient should proceed to angiography/surgery without noninvasive testing. In a nonthreatened limb with suspected occlusion, ABIs can be performed along with a duplex scan. A duplex scan can help to identify the source of occlusion or confirm a thrombotic event, such as in the territory of a peripheral aneurysm or a stenosis (Fig. 5).

Traditionally, arteriography has been the *gold standard* for diagnosis of arterial disease. The recent advancement of duplex scanning has enabled some centers to perform lower extremity revascularization procedures without angiography. Several studies in the last decade have shown

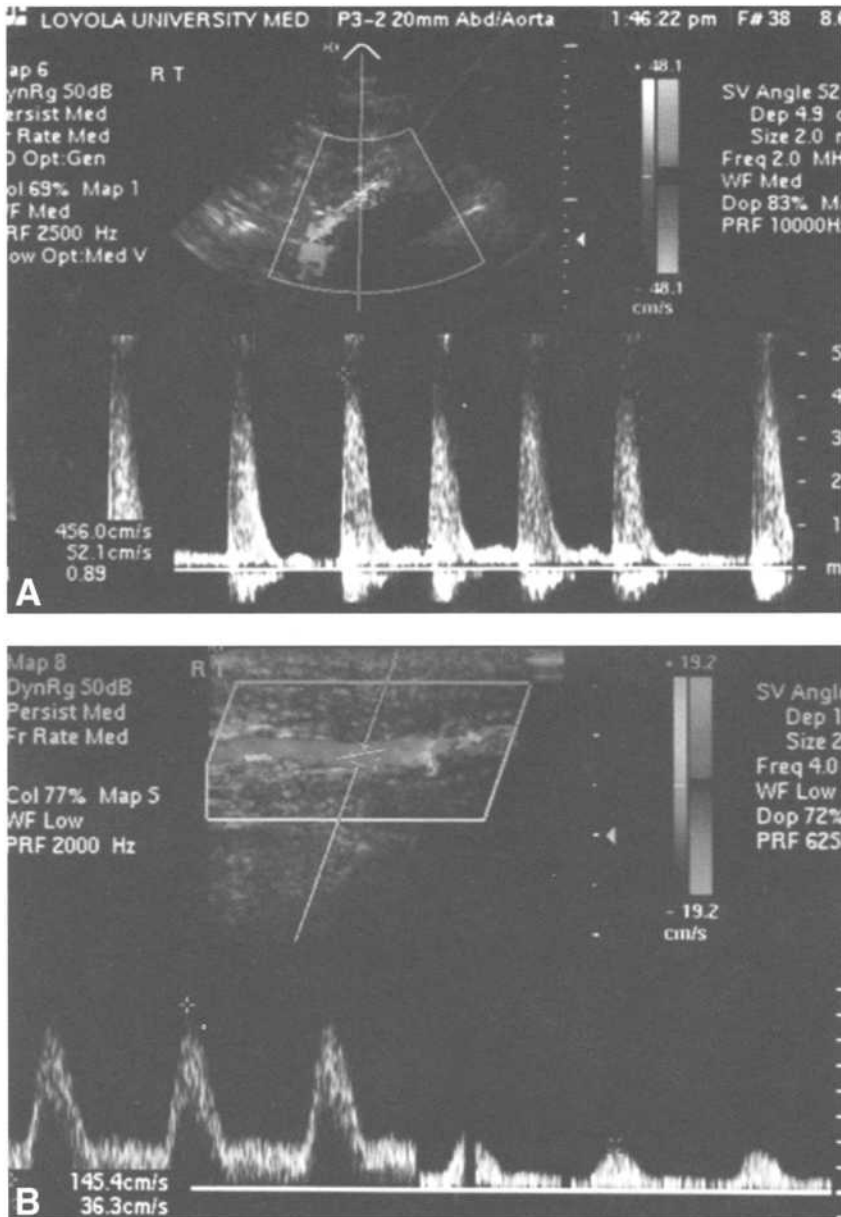


Fig. 2. Significant stenosis in peripheral arteries. **(A)** Stenosis in the common iliac artery. Both the peak systolic and end diastolic velocities are significantly increased. The V_2/V_1 was 3.9 (456/117) indicating a $>50\%$ diameter stenosis. **(B)** Stenosis in the anterior tibial artery. The prestenotic (36 cm/s) and the poststenotic (145 cm/s) velocities are obtained to estimate the V_2/V_1 ratio (4.0).

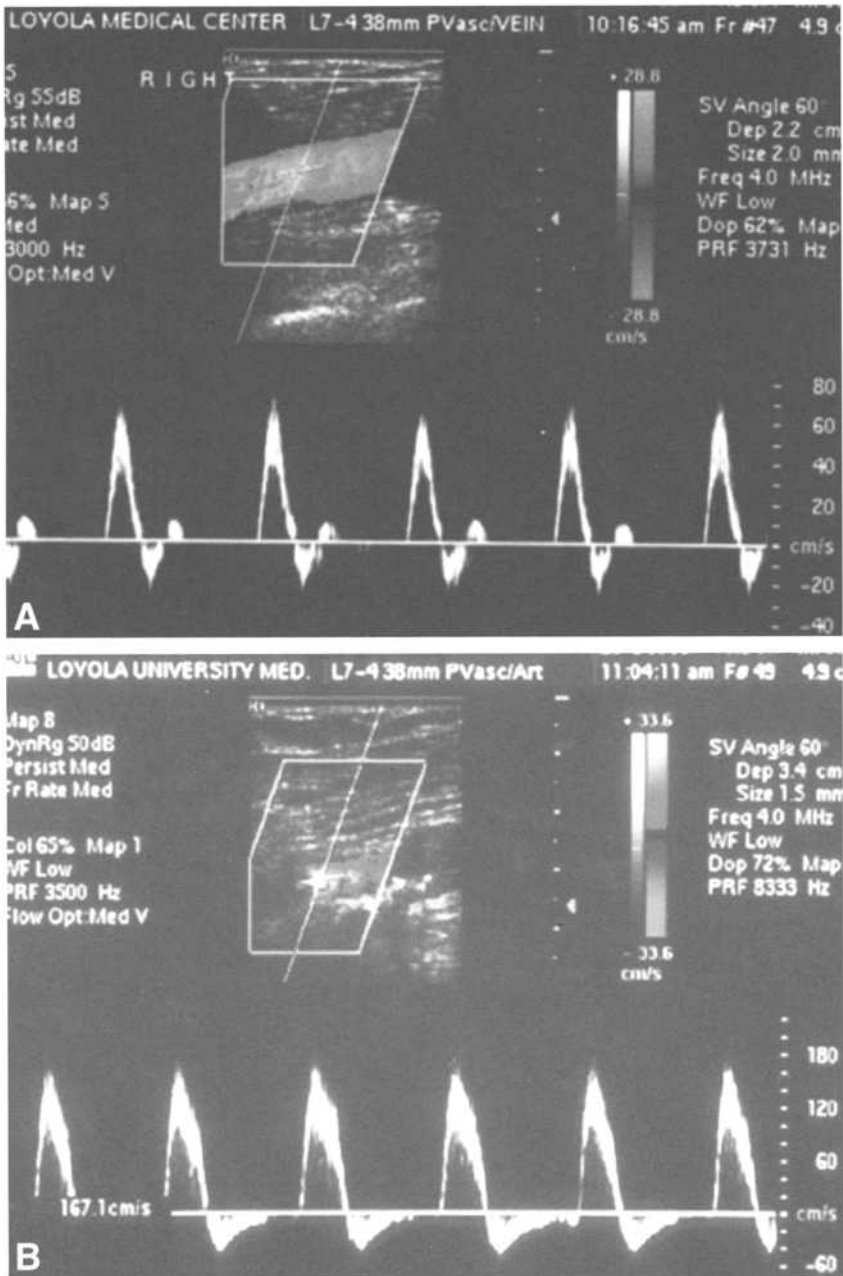


Fig. 3. Prediction of iliac stenosis from the common femoral artery (CFA) waveform. (A) triphasic waveform in the CFA indicates normal ipsilateral iliac arteries. (B) Biphasic waveform indicates mild to moderate (continued on page 32)

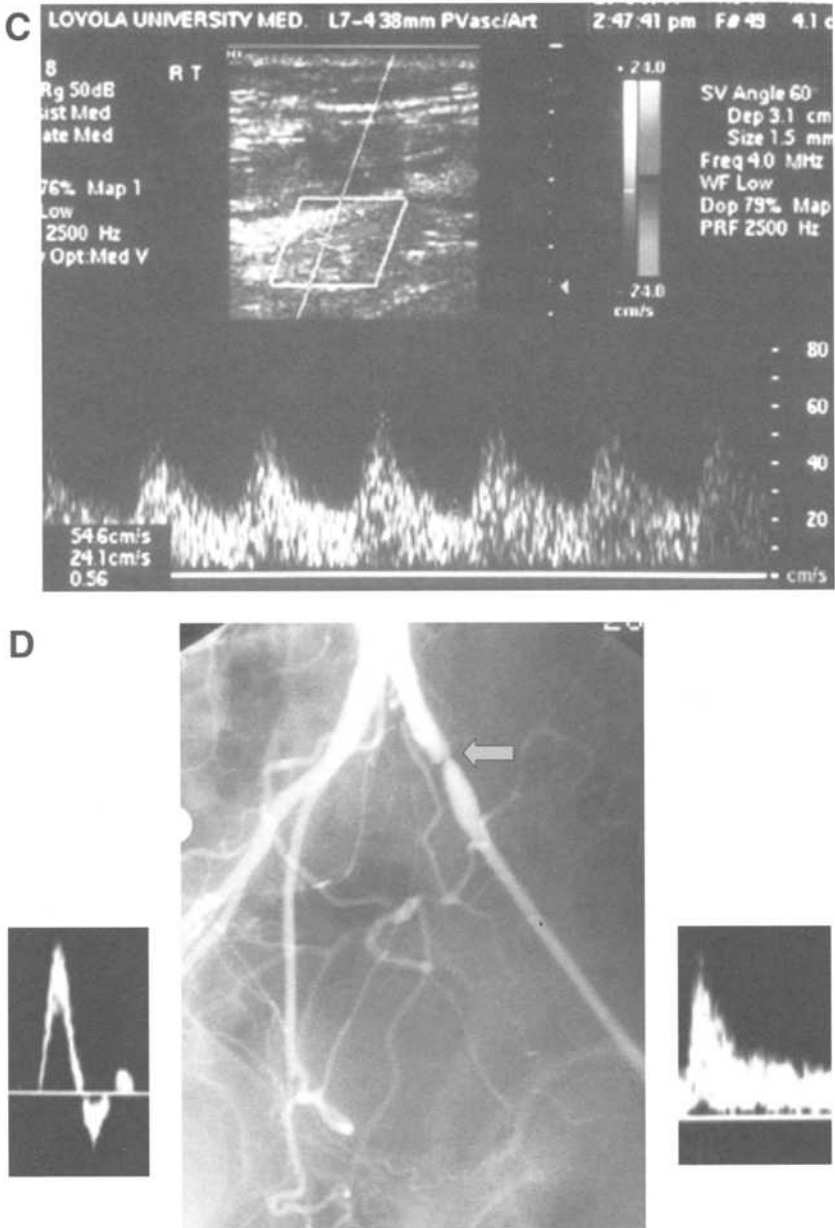


Fig. 3. (continued from page 31) stenosis. **(C)** Monophasic waveform denotes the presence of significant stenosis or occlusion. **(D)** Angiography and duplex scanning in a patient with intermittent claudication in the left lower extremity. In the right lower extremity the waveform is triphasic and the ipsilateral iliac artery in the angiogram is normal. In the contralateral limb the waveform is monophasic and a significant stenosis is present in the ipsilateral iliac artery (solid arrow).

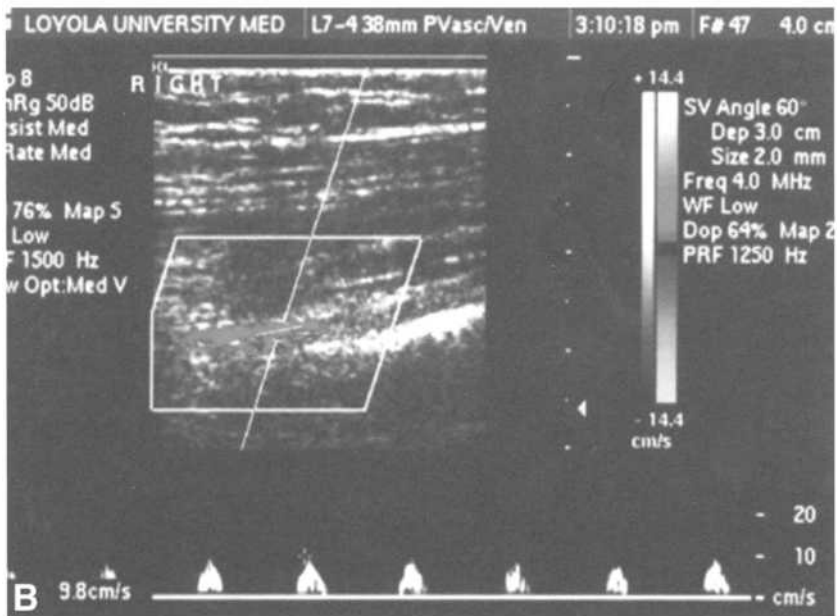
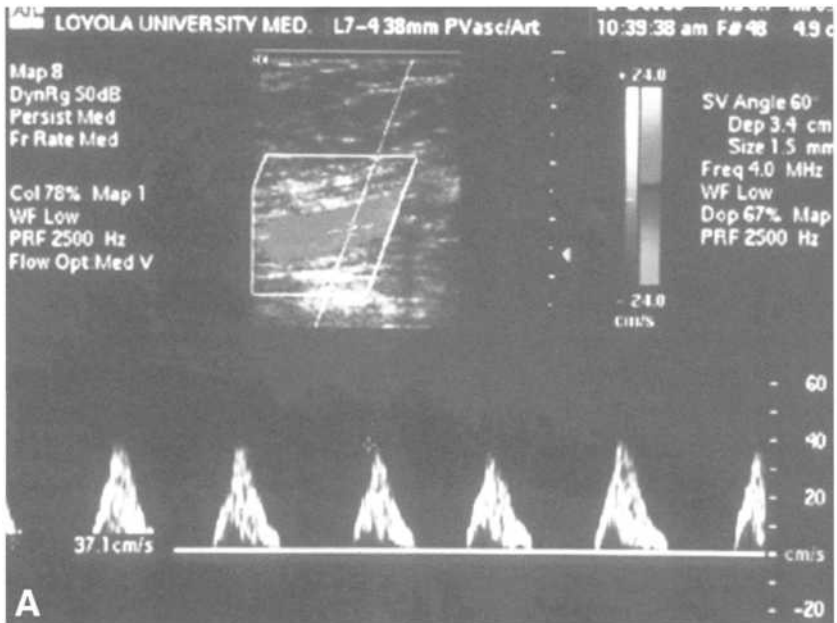


Fig. 4. Low amplitude waveform with absence of end diastolic velocity is common in patients with occluded arterial segments above and below the segment under investigation. **(A)** Low amplitude and absence of end diastolic velocity in the superficial femoral artery in the mid-thigh in a patient with common iliac significant stenosis and distal superficial femoral artery occlusion. **(B)** Very low velocities and a monophasic waveform in the posterior tibial artery of a patient with multiple stenoses and occlusions proximal and distal to the site of measurement.

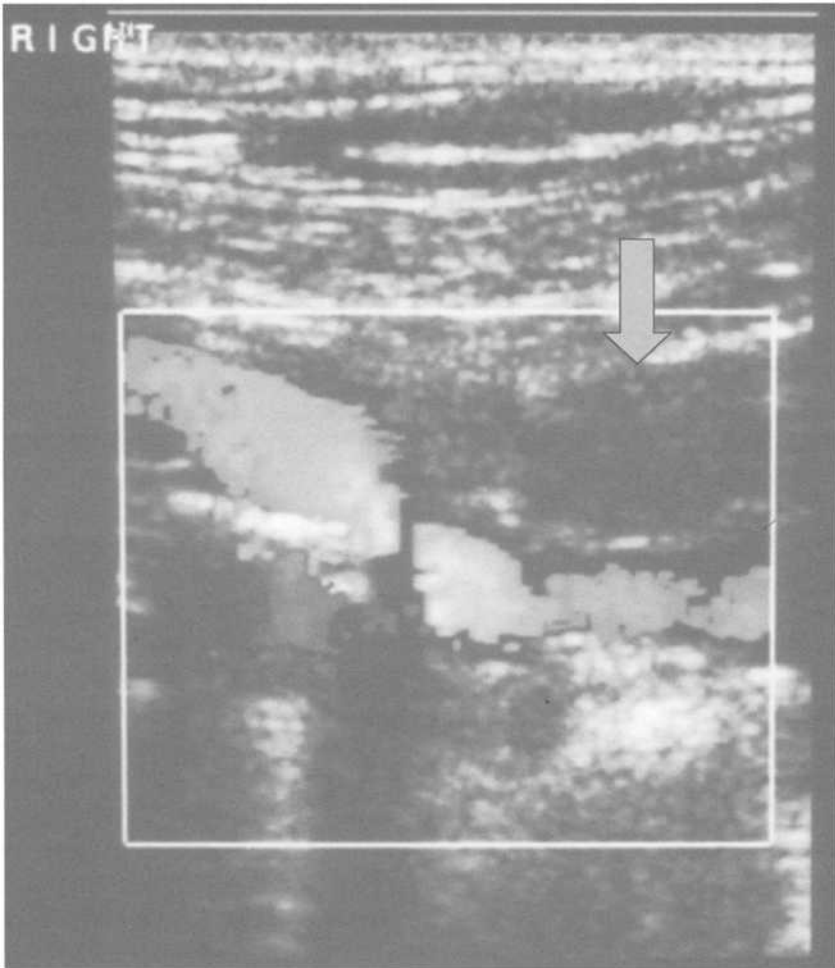


Fig. 5. Acute thrombosis of the right external iliac artery (solid arrow) in a patient with atrial fibrillation. The common iliac and internal iliac arteries are patent. The patient presented with acute lower ischemia. A thrombectomy was performed and the symptoms were resolved.

very promising results on that application. Duplex scanning can also be used with great accuracy in determining whether an iliac lesion is a good target for percutaneous intervention. The length of the lesion, degree of stenosis, and amount of calcification can all be accurately evaluated, giving the physician valuable information for decision making. In addition, duplex can be used to determine the presence of distal targets for revascularization procedures when none are visible by angiography (Fig. 6).

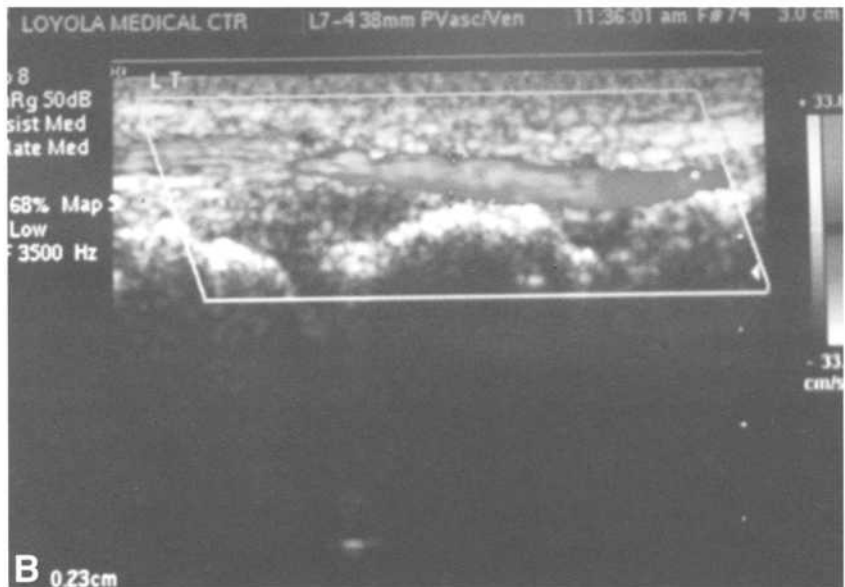
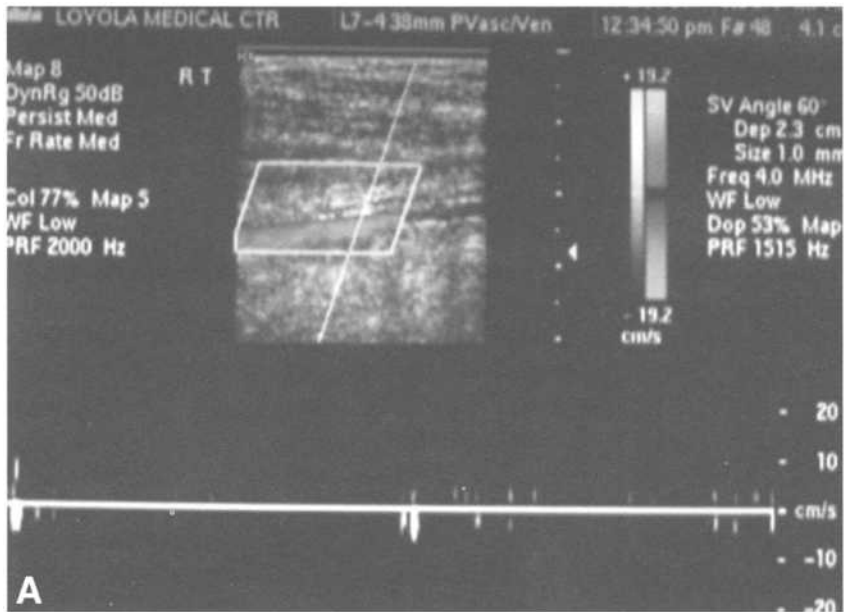


Fig. 6. Target arteries for surgery can be selected with the duplex scanning. Arterial segments with stenosis, diffused disease and heavy calcification are not selected for the distal anastomosis. **(A)** Occluded, calcified posterior tibial artery. **(B)** The dorsalis pedis artery in this patient had no significant abnormality and it was the best artery for the bypass placement. This was a diabetic patient with typical infrapopliteal disease that underwent a popliteo-tibial by-pass with a saphenous vein.

Magnetic Resonance Angiography

In recent years, magnetic resonance imaging (MRI) and magnetic resonance arteriography (MRA) have been employed with increased frequency as diagnostic tools in the management of peripheral arterial disease (18).

BASIC PRINCIPLES

MRI is based on the reactions of various tissues to a magnetic field followed by a radiofrequency radiation pulse. MRA imaging is generated by taking advantage of blood flow-related effects relative to the stationary surrounding soft tissues. Two techniques are currently used for MRA:

Time of flight (TOF) angiography: TOF MRA relies on signal difference between stationary protons in the vessel wall and the surrounding soft tissues, compared to moving protons (flowing blood).

Phase contrast (PC) angiography: Protons undergo a change in the phase of their rotation as they move through a magnetic field. PC MRA uses gadolinium that shortens the T1 relaxation of blood protons, thereby increasing the intravascular signal.

Background can be eliminated by subtraction protocols and its suppression is greater for PC than for TOF MRA. Because of inherent limitations, TOF MRA has never become a real alternative to contrast angiography except in very few highly experienced centers. Currently, PC MRA is considered the best alternative to contrast angiography.

CLINICAL APPLICATIONS

MRA has evolved as a noninvasive, sensitive accurate, and cost-effective method of imaging of the peripheral arterial circulation. Although contrast angiography is still considered the gold standard, it carries an overall (major and minor) complication rate of approximately 8%. Local complications related to the arterial puncture (bleeding, hematoma, infection, thrombosis, stenosis, pseudoaneurysm, etc.) and systemic complications (contrast-induced allergic reactions or renal insufficiency) are not uncommon. MRA is an alternative noninvasive imaging method for the peripheral vessels that avoids the risk of these complications. Its sensitivity in and specificity in detecting patent segments, hemodynamically significant stenoses and/or occlusions approaches 100%. In a recent review of the existing literature, TOF MRA was found to have sensitivity and specificity of 82% and 84%, respectively, whereas PC MRA had a 96% sensitivity and specificity compared to conventional angiography (18). The latter was also reported to be more sensitive in detecting patent distal run-off vessels in patients

with severely compromised distal circulation. This advantage is inherent to the mechanism of image formation in MRA, which requires only the presence of local flow with velocity as low as 2 cm/s. Presently, MRA is considered the imaging modality of choice for the diagnosis of vascular arterio-venous malformations and popliteal entrapment syndrome. In several centers, MRA is used as the sole pre-operative imaging technique for distal revascularization procedures with great success. It is currently considered to be more cost-effective compared to contrast angiography.

Nevertheless, not all patients are suitable for MRI/MRA exams. Individuals with implanted metal devices (pacemakers, cerebral vascular clips, etc.) should not be considered for such imaging. Claustrophobia remains a relative contraindication. The exam may also be limited by respiratory movements, but with contrast-enhanced MRA the acquisition time has significantly decreased (approximately 20 seconds for a complete limb exam), making *breath-hold images* possible.

REFERENCES

1. Bernstein EF. Vascular Diagnosis, 3rd edition, St. Louis, 1993.
2. Myers KA, Scott DF, Devine TJ, Johnston AH, Denton MJ, Gilfillan IS. Palpation of the femoral and popliteal pulses: a study of the accuracy as assessed by agreement between multiple observers. *Eur J Vasc Surg* 1987;1:245–249.
3. AbuRahma AF, et al. Lower Extremity Arterial Evaluation: Are segmental arterial blood pressures worthwhile? *Surgery* 1995;118:496–503.
4. Labropoulos N, Volteas N, Giannoukas A, Kutoubi A Al, Wolfe J, Mansfield AO, Nicolaides AN. Early hemodynamic effects of percutaneous transluminal angioplasty in patients with superficial femoral artery disease. *Vasc Surg* 1997;31:615–621.
5. Androulakis AE, Labropoulos N, Allan R, Tyllis TK, Kutoubi A Al, Nicolaides AN. The role of common carotid artery end-diastolic velocity in near total or total internal carotid artery occlusion. *E J Vasc Endovasc Surg* 1996;11:140–147.
6. Sumner DS. Essential hemodynamic principles. In: Rutherford RB, ed. Vascular Surgery, 4th ed. Philadelphia:W.B. Saunders Company 1995, pp. 18–44.
7. Taylor PR, Tyrrell MR, Crofton M, Bassan B, Grigg M, Wolfe JH, Mansfield AO, Nicolaides AN. Colour flow imaging in the detection of femoro-distal graft and native artery stenosis: improved criteria. *Eur J Vasc Surg* 1992;6:232–236.
8. Williams MA, Nicolaides AN. Predicting the normal dimensions of the internal and external carotid arteries from the diameter of the common carotid. *Eur J Vasc Surg* 1987;1:91–96.
9. Attinger EO, Sugawara H, Navarro A, et al. Pressure flow relations in dog arteries. *Circ Res* 1966;19:230.
10. May AG, Van deBerg L, DeWeese JA, et al. Critical arterial stenosis. *Surgery* 1963;54:250.
11. Moore WS, Malone JM. Effect of flow rate and vessel caliber on critical arterial stenosis. *J Surg Res* 1979;26:1.
12. Burger R, Hwang NHC. Critical arterial stenosis. A theoretical and experimental solution. *Ann Surg* 1974;180:39

13. Giannoukas AD, Androulakis A, Labropoulos N, Wolfe J. The role of surveillance in the lower limb bypass graft. *E J Vasc Endovasc Surg* 1996;11:279–289.
14. Koelmay MJ, den Hartog D, Prins MH, Kromhout JG, Legemate DA, Jacobs MJ. Diagnosis of arterial disease of the lower extremities with duplex ultrasonography. *Br J Surg* 1996;83:404–409.
15. Elsman BH, Legemate DA, de Vos HJ, Mali WP, Eikelboom BC. Hyperaemic colour duplex scanning for the detection of aortoiliac stenoses. A comparative study with intra-arterial pressure measurement. *Eur J Vasc Endovasc Surg* 1997;14:462–467.
16. Labropoulos N, Androulakis A, Allan R, Touloupakis E, Kutoubi A Al, Nicolaidis AN. The value of colour flow duplex imaging in the detection of subtotal and total internal carotid artery occlusion. *Vasc Surg* 1997;775–779.
17. Eiberg JP, Jensen F, Gronvall Rasmussen JB, Schroeder TV. Screening for aortoiliac lesions by visual interpretation of the common femoral Doppler waveform. *Eur J Vasc Endovasc Surg* 2001;22:331–336.
18. Eiberg JP, Lundorf E, Thomsen C, Schroeder TV. Peripheral Vascular Surgery and Magnetic Resonance Angiography: a Review. *Eur J Vasc Endovasc Surg* 2001;22:396–402.

3

Smoking and Smoking Cessation

Albert J. Bellg, PhD
and Aristdis N. Mavridis, MD, FCCP

CONTENTS

INTRODUCTION
SMOKING AND CARDIOVASCULAR DISEASE RISK
PHYSIOLOGICAL MECHANISMS INCREASING RISK
OF CARDIOVASCULAR DISEASE FROM SMOKING
BENEFITS OF SMOKING CESSATION
SMOKING CESSATION ISSUES
PHYSICIAN-DELIVERED SMOKING CESSATION
PROGRAMS
REFERENCES

INTRODUCTION

When Christopher Columbus discovered America he found the natives chewing tobacco in much the same manner as is done today (1). The American Indians believed tobacco to have medicinal properties, and it was also used in native ceremonials in the New World. Once in Europe, the genus *Nicotiana* was named in honor of Jean Nicot, the French ambassador to Lisbon, who sent the seeds of *Nicotiana tabacum* to Catherine de Medicis, the queen of France. The word *tobacco* was derived from an American Indian word referring both to a tube for inhaling the smoke and to a cylinder of leaf prepared for smoking.

The association of smoking with health problems is almost as old as the use of tobacco. In 1604, King James I of England issued the first

From: *Clinical Hypertension and Vascular Diseases: Lower Extremity Arterial Disease*
Edited by: D. G. Caralis and G. L. Bakris © Humana Press Inc., Totowa, NJ

official condemnation of tobacco, "A Counterblaste to Tobacco." In 1859, it was shown that of 68 patients in a Montpelier hospital in France who had cancer of the lips, tongue, tonsils, or other parts of the mouth, all used tobacco; 66 of them smoked short-stemmed clay pipes. The earliest concern about the danger of cigaret-smoking based on modern scientific methods developed in the late 1940s, when it was realized from case-control studies that smoking is causally related to lung cancer. In 1954, the American Cancer Society and the British Medical Research Council reported independently that death rates were higher for cigaret smokers than for nonsmokers. In 1964, the Surgeon General of the United States published the landmark "Report on Smoking and Health," which was updated in 1979. This report reinforced more strongly than ever that cigaret smoking is one of the most serious health hazards faced by Americans (2). The consequences of smoking have been regularly reviewed by the US Public Health Service in publications of the National Clearinghouse on Smoking and Health, as well as by other authorities (3-7).

There is currently near-consensus in the medical community on the hazards of smoking. Approximately 430,700 American smokers died of premature illness each year on average from 1990-1994 (8). The Centers for Disease Control and Prevention has estimated that the health care costs associated with tobacco are about \$50 billion annually, with an additional estimated \$80 billion added if one includes the cost of smoking during pregnancy, lost workdays, lost output from early death and retirement, and fires caused by smoking (9). In the general population, most people are aware of the link between smoking and cancer; far fewer are aware of the relationship between smoking and heart disease and vascular diseases in general. Nonetheless, the risk of morbidity and mortality from coronary artery disease, stroke, sudden cardiac death, and peripheral vascular disease has been linked to cigaret smoking in many cross-cultural and national studies (10,11).

SMOKING AND CARDIOVASCULAR DISEASE RISK

The risk of heart disease is directly related to the number of ciga­rets smoked (12). Smoking one pack of ciga­rets per day doubles the risk for heart disease, whereas smoking more than one pack per day triples the risk. Cigaret, cigar, and pipe smoking, chewing tobacco and snuff, as well as occupational exposure to environmental tobacco smoke and passive smoking at home, are all deleterious to health (13-15).

In addition, risk and type of cigaret are only loosely associated; there are no *safe* ciga­rets. In a study of more than a million men and women from 1960 to 1972 (16), the health consequences of smoking high-tar

and high-nicotine cigarettes were compared to the effects of smoking brands lower in tar and nicotine. Although total death rates were somewhat lower for low-tar and low-nicotine brand smokers than for smokers of high-tar and high-nicotine brands, those death rates were still 30 to 75% higher than those of nonsmokers. Lower-tar and low-nicotine cigarettes are not *safe*.

Nonsmokers who live with or work with smokers are also at risk. It has been estimated (17–19) that there are 35,000 to 40,000 annual excess heart disease deaths among never-smokers and long-term former smokers as a result of their exposure to environmental tobacco smoke. By comparison, lung cancer has been estimated to cause approximately 3000 excess deaths per year among never-smokers. A census of Washington County, Maryland, in 1963 obtained information on smoking habits of all adults in the census; death certificates of all residents who died in the subsequent 12 years were coded for underlying cause of death and matched to the census (20). Death rates from coronary heart disease of nonsmokers were higher among men and women who lived with smokers, as compared with those living with nonsmokers.

Smoking also contributes to the prevalence of stroke in the United States. Several large prospective studies, including the Framingham Study, have linked smoking to stroke generally and to specific stroke types, including brain infarction, intracerebral hemorrhage, and subarachnoid hemorrhage (21). In the Framingham Study, even after other risk factors were taken into account, stroke incidence was 40% higher in male smokers and 60% higher in female smokers compared with nonsmokers. The impact of smoking on stroke did not decrease with advancing age. However, within 2 years of quitting smoking, the risk of stroke fell significantly. Within 5 years of quitting cigarette smoking the risk of stroke fell to that of a nonsmoker.

For large vessel peripheral arterial disease, cigarette smoking is the most important risk factor (22). Surgical revascularization is significantly less effective in reducing long-term symptoms of claudication if patients continue to smoke.

PHYSIOLOGICAL MECHANISMS INCREASING RISK OF CARDIOVASCULAR DISEASE FROM SMOKING

There are strong plausible hypotheses for the relation between exposure to tobacco and vascular disease. In animal and human studies, endothelial injury has been associated with carbon monoxide and nicotine. In contrast to healthy individuals, those with ischemic heart disease are affected by carbon monoxide during submaximal exercise, in part

because carbon monoxide reduces the ability of hemoglobin to combine with oxygen and diminishes oxygen transport from the lungs to the tissues. Levels as low as 2.5 to 3% carboxyhemoglobin (COHb) have been found to decrease exercise time before the onset of angina and prolong the duration of ischemia. For maximal exercise, the critical level is approximately 4.5% COHb. Above this level, both exercise and VO₂max are inversely related to CO concentration. Additionally, cigarette smokers may have baseline COHb in the 4 to 8% range (23).

Platelet and clotting factors predisposing to formation of thrombus, as well as vascular smooth muscle cell proliferation have also been observed with exposure to cigarette vapor components, including carbon monoxide and nicotine. Increased platelet aggregation has been found both in humans and in animals (24,25). Thrombolytic substances such as plasminogen have been found to be lower in smokers and to increase with cessation of smoking (26,27).

There is a growing body of evidence suggesting that oxidation of low density lipoprotein (LDL)-cholesterol particles may be a pivotal step in atherogenesis (28–30). Cigarette smoking, even for brief periods, can markedly enhance LDL-cholesterol oxidation as well as decrease high-density lipoprotein cholesterol (31). It also depletes body stores of vitamin C that may be an important antioxidant protection. Intake of the anti-oxidant beta carotene has been shown to be inversely related to the risk of coronary events among current smokers (relative risk 0.30) and former smokers (relative risk 0.60), but was not beneficial in persons who had never smoked (32,33).

Fibrinogen has also been implicated in atherogenesis and thrombus formation, and has been found to be elevated in smokers (34,35). The Framingham Study has shown that risk of cardiovascular disease (CVD) and stroke increased with increases in fibrinogen levels. In this study, as well as in other studies, smokers had a higher risk of developing claudication compared with nonsmokers with similar risk factor profiles (17,36–40).

Cigarette smoking can cause marked coronary vasoconstriction (41,42), and has been strongly associated with angiographically documented coronary spasm in men and women (43–45). Vascular endothelial damage from smoking can cause thromboxane A₂ release, decreased prostacyclin production, α -adrenergic stimulation, and vasopressin generation in the process of provoking constriction of the coronary vessel. Cigarettes elevate the circulating level of catecholamines and free fatty acids that can further alter vascular tone.

Smoking also:

- Decreases the useful blood levels of drugs like β -blockers as a result of their increased metabolism (46).
- Increases both blood pressure and heart rate.
- Lowers the threshold for ventricular arrhythmias (13).
- Has a direct toxic effect on the ventricular myocardium (47,48) and may significantly increase myocardial oxygen demand.

Passive smoking is also associated with dose-related impairment of endothelium dependent dilatation, suggesting early arterial damage (49). Studies have concluded that the public health burden caused by environmental tobacco smoke (ETS) is likely to be much greater for heart disease than for lung cancer (50). Although environmental tobacco smoke is less dense, it is more toxic. Twice as much nicotine is emitted in sidestream as in mainstream smoke, and the ratio for benzene is 10:1. The concentration of carbon monoxide is 2.5 times higher in sidestream smoke than it is in mainstream smoke. Polycyclic aromatic hydrocarbons present on smoke as well as in environmental air pollution are capable of inducing and accelerating atherosclerosis. Tobacco smoke may also sensitize circulating neutrophils in humans, and may cause their subsequent activation and oxidant-mediated tissue damage, leading to atherosclerosis of the coronary and peripheral vessels (51).

BENEFITS OF SMOKING CESSATION

Smoking cessation significantly improves cardiovascular health. According to the World Health Organization, within 1 year of quitting the risk of CHD decreases by 50%, and within 15 years (and often less) the relative risk of dying of CHD for an ex-smoker approaches that of a long-time nonsmoker (8,52). Therefore, smoking cessation is more beneficial in reducing mortality in the aggregate of smokers with coronary artery disease than medical therapy, β -blockers with bypass surgery, or coronary angioplasty (53,54).

Short of revascularization, cessation of smoking is the single most important factor in the management of patients with intermittent claudication (55). In fact, in up to 85% of patients, walking distance can increase as much as 200 to 300% (56,57). Detection and treatment of hypertension and control of risk factors for cardiovascular disease such as smoking, diabetes, and hyperlipidemia offer substantial stroke prevention benefits as well.

SMOKING CESSATION ISSUES

As Mark Twain said, “Quitting smoking is easy—I have done it many times.” Although the health benefits of smoking cessation are substantial and would seem to provide all the motivation a smoker would need to quit, long-term smoking cessation remains among the most difficult behavioral changes to sustain.

Since 1965, smoking has declined gradually by about 42%, but recent data indicate that this downward trend may have leveled off (8). In the United States, approximately 25.9 million men and 22.8 million women 18 years and older are smokers, about one in four in the adult population. Smoking rates are highest in adults with less than 9–11 years of education (39.7% of men, 34.3% of women), and lowest in those with 16 or more years of education (11.5% of men, 11.2% of women). Non-Hispanic black men are marginally more likely to smoke than non-Hispanic white men (29% vs 24.7%). American Indians/Alaskan Natives are also more likely to be smokers (41.7% of men, 38.1% of women) (8).

Most people who quit do so on their own. Those who repeatedly attempt to quit and fail are often discouraged and frequently require professional assistance in dealing with the powerful physiological and behavioral responses associated with smoking.

Physical dependence on nicotine is one of the two major factors driving people to their smoking behavior. In 1988, the Surgeon General’s report on nicotine addiction contended that cigaret smoking meets all of the established criteria for drug addiction, that nicotine is the psychoactive drug responsible for the addiction, and that cigaret smoking is similar to cocaine abuse in terms of the behavior associated with its maintenance. Each cigaret puff delivers a dose of nicotine to the brain within 7 seconds. Thus, smoking is one of the most rapid drug delivery systems. A smoker may self-administer 50,000 to 70,000 doses of nicotine per year.

Withdrawal from nicotine can produce several effects, including craving for tobacco, anxiety, irritability, increased restlessness, difficulty in concentrating, headache, drowsiness, and gastrointestinal symptoms. These symptoms are particularly pronounced for 2 to 3 days after cessation, but usually cease after that time. It is important to note that withdrawal symptoms *per se* are not generally associated with or triggered by specific situations, although they may be more or less severe during the withdrawal period and medications and behavioral coping strategies may reduce their intensity. These general withdrawal symptoms must be

distinguished from specific conditioned cravings for cigarettes that can continue for months or even years after withdrawal has been completed.

Psychological addiction is the second major factor involved in sustaining smoking behavior and is not directly related to the ex-smoker's previous physical dependency on nicotine. A classical conditioning model can explain much of the craving for cigarettes that can occur long after an ex-smoker has gone through nicotine withdrawal. Repeated association of smoking (an unconditioned stimulus) with using a telephone, driving a car, drinking a cup of coffee, working at a computer, etc. can lead to these activities becoming associated with the thought or memory of cigarettes and even with the physiological response to smoking (thus becoming conditioned stimuli). Smokers can also become conditioned to smoke during subjective experiences such as stress, depression, anxiety, boredom, or anger. The result of this conditioning is that the exsmoker can be reminded of smoking or experience a physiological craving for a cigarette when exposed to the normal daily activities or subjective experiences during which he or she had been accustomed to smoke.

In addition, different factors may be involved in ex-smokers who relapse after several months or years of abstinence. Relapse may result from encountering social pressure to smoke, an unaccustomed stressor such as a personal loss, or an unexpected situation that leads to a return to smoking. A key concept in preventing relapses is the distinction between a *lapse*, which is a brief use of cigarettes, and a *relapse*, which is a full return to smoking in the pattern previously followed by the smoker. One of the main goals of relapse prevention is to keep a lapse from turning into a relapse.

The following recommendations for an outpatient medical clinic-based smoking cessation protocol follow current US Public Health Service recommendations (58), with additional suggestions to specifically distinguish and address both nicotine withdrawal symptoms, conditioned cravings for cigarettes, and relapse prevention.

PHYSICIAN-DELIVERED SMOKING CESSATION PROGRAMS

In 1991, 70% of smokers in the United States had at least one outpatient visit with a physician or other health professional during the previous year (59). Sixty to 70% of current smokers want to stop; 70 to 80% feel that a physician intervention would help them in quitting. There is a natural window of opportunity for physicians to intervene with smok-

ers, and the effectiveness of physician advice is cost-effective and has been examined in trials of smokers in general practice (60).

However, simple advice by the physician to quit smoking compared to no advice, results in only an additional 5% of smokers quitting in 1 year. Physicians are not unaware of this low rate of success, and unfortunately it has resulted in many physicians not systematically addressing smoking with their patients. Having a more effective yet practical smoking cessation protocol is likely to increase physician attention to this issue.

The following clinical practice guideline for smoking cessation is based on the guidelines recommended by the United States Public Health Service (58). It suggests that *every* patient who smokes be offered an intervention for smoking. Patients who are willing to quit now should be provided with effective treatment; patients who are *unwilling* to quit now should be provided with a brief intervention designed to increase their motivation and readiness to quit.

Step 1: Ask About Tobacco Use

Clinicians should ask all patients whether or not they smoke. The goal is to screen for and identify patients in three categories:

1. Smokers who are willing to make a quit attempt within the next 30 days
2. Smokers who are unwilling to make a quit attempt at this time
3. Former smokers

Step 2: Advise All Smokers to Quit

All smokers should be advised to quit in a clear, strong, and personalized manner. At the same time, acknowledge that it is up to the patient to make the decision to quit. Ask the patient what their personal reasons for quitting might be. Look for reasons that are concrete, specific, and personal such as, "I want to be able to keep up with my grandchildren when we go to the zoo." Theoretical, vague, and impersonal reasons may sound like the *right* answer ("I want to quit for my health"), however, they are less likely to motivate behavior.

Step 3. Assist Smokers Willing to Quit Within the Next 30 Days

1. Discuss a *quit plan* with patients. The patient should:
 - a. Set a quit date (ideally, within 2 weeks).
 - b. Tell family, friends, and coworkers about quitting and request support.

- c. Anticipate what to do to meet challenges that occur, such as withdrawal symptoms and conditioned cravings.
 - d. Remove tobacco products from their environment prior to quitting.
2. Provide practical counseling and problem solving.
 - a. Total abstinence is essential. “Not a single puff past the quit date.”
 - b. Find other ways to accomplish the positive things that smoking does for the patient, such as provide relief from stress and boredom, keep weight down, aid in socializing with friends who smoke, etc.
 - c. Review past quit attempts to identify what helped during the quit attempt and what lead to relapse.
 - d. Based on past experience and the patient’s self-knowledge, discuss challenges to staying smoke-free and how the patient will overcome them. Discuss specific issues such as using alcohol without smoking or quitting while other smokers are in the house.
3. Provide support for patient.
 - a. Encourage patient to use clinic staff for advice and assistance during the quit period, particularly during the first week after quitting smoking. A daily phone call or brief clinic visit during the first several days (the withdrawal period) can be particularly helpful to the patient.
 - b. Encourage patient to obtain support from family and friends.
4. Recommend use of approved pharmacotherapy to reduce symptoms of withdrawal and increase smoking cessation success, except when contraindicated by the patient’s medical condition. There are five first-line approved medications:
 - a. Bupropion SR (Zyban). 150 mg QD for 3 days, then 150 mg BID for 4 weeks up to 6 months. Contraindications: history of seizures, history of eating disorder.
 - b. Nicotine replacement therapy in the form of the patch, gum, nasal spray, or inhaler. Generally used for 3–6 months. Initiate dose of nicotine replacement therapy at approximately the level of the smoker’s current daily nicotine consumption. Note that nicotine replacement, in particular the nicotine patch, is safe and has not been shown to cause adverse cardiovascular effects (58). Second-line pharmacotherapy (clonidine or nortriptyline) may be used if first-line therapies are contraindicated.
5. Recommend use of behavioral techniques to deal with stress, withdrawal symptoms, and conditioned cravings for cigarettes.
 - a. Use deep breathing and relaxation to make withdrawal symptoms easier and eliminate conditioned cravings.
 - b. During withdrawal, also have patient distract himself or herself with other activities when feeling uncomfortable.
 - c. Confront specific conditioned cravings by having the patient deliberately place himself or herself in the situation that evokes a craving,

and then breathe deeply and relax to make the craving go away. Repeat until the situation no longer evokes a craving. Generally, this should be done after the 3-day withdrawal from nicotine.

- d. Recommend using a *nonsmoking break* for stress management. This is designed to mimic the behavioral stress management components of taking a smoke break, but without a cigaret. There are three steps: (1) get away from the stressor, (2) distract oneself with a minor activity, and (3) take several deep breaths to relax.
6. Provide supplementary information and brochures that are culturally, racially, and age appropriate for the patient.

Unless a patient has had a good experience in the past quitting with nicotine replacement therapy or is not able to tolerate Zyban, we generally do not recommend nicotine replacement in our clinic and suggest that the patient's *quit day* be the day they begin their 3-day withdrawal from nicotine. This allows the patient to deal with withdrawal *up front* during a well-defined period that includes daily clinical contact by telephone or in person and pharmacotherapy assistance from Zyban. It is our experience that patients on nicotine replacement therapy are at increased risk of resuming smoking when they finally quit nicotine replacement, and go through withdrawal several weeks or months after their quit day.

Although Zyban is generally recommended for approximately 3 to 4 months following smoking cessation, when medication costs are a consideration we have found that patients find it helpful in reducing withdrawal symptoms when they use it for as little as 2 to 4 weeks (starting about 4 days prior to the quit day). Close contact with the patient during the first several days after quitting smoking is essential, and we recommend a daily phone call to an identified clinic staff person to report on difficulties and obtain support.

Step 4. Provide a Motivational Intervention for Smokers Currently Unwilling to Quit

With smokers unwilling to quit, have a brief discussion following the 5 Rs: relevance, risks, rewards, roadblocks, and repeat as necessary at future clinic visits.

1. Relevance. Have patient indicate their own personal reasons for quitting smoking, being as concrete and specific as possible.
2. Risks. Ask the patient to identify potential negative health consequences of tobacco use. Discuss acute, long-term, and environmental risks.

- a. Acute risks: shortness of breath, exacerbation of asthma, harm to pregnancy, impotence, infertility, etc.
 - b. Long-term risks: myocardial infarction (MI) and stroke, peripheral vascular disease, lung and other cancers, etc.
 - c. Environmental risks: increased risk of heart disease and lung cancer in spouses; higher rates of smoking in children of smokers; sudden infant death syndrome, asthma, middle ear disease, respiratory infections in children of smokers.
3. Rewards. Ask the patient to identify the specific benefits that may come from quitting smoking, such as improved taste and smell, better-smelling car and clothing, feeling better physically, etc.
 4. Roadblocks. Ask the patient to identify barriers to quitting (such as fear of withdrawal symptoms, weight gain, depression, enjoyment of tobacco, etc.), and use problem solving to try to address issues.

Step 5. For Former Smokers, Assist in Preventing Relapse

Relapse prevention involves anticipating potential difficulties that may lead to resumption of smoking and addressing them in advance as much as possible. Issues to be dealt with may include:

1. Feeling a lack of support from family and friends
2. Negative mood or depression
3. Weight gain, expected or unexpected
4. Prolonged conditioned cravings or difficulty withdrawing from nicotine replacement therapy
5. Flagging motivation or feeling deprived
6. Keeping a *lapse* from evolving into a *relapse*

In regards to keeping a lapse from becoming a relapse, patients should be specifically told that if circumstances lead them to smoke one or two cigarettes, they have not failed and can choose to go back being smoke-free. The worst situation is for them to smoke a single cigarette, decide they have failed, and resume smoking at their previous level. An effective analogy to use is as follows: “If circumstances lead you to say something you wish you hadn’t said to a person, you don’t need to go on saying it. The same thing applies if circumstances lead you to smoke one or two cigarettes.” Simultaneously with this message, however, patients should be explicitly told that this does not imply that they are being given *permission* to smoke one or two cigarettes occasionally; their health does not benefit if they become occasional smokers, and their risk of complete relapse rises substantially.

Step 6. If Necessary, Refer Patient to a Professional Smoking Cessation Program

Structuring a clinic to provide patients with an effective and comprehensive smoking cessation program may not always be possible. However, we contend that it is *always* possible to provide a referral to such services when smokers have been identified and the risks of continuing to smoke have been discussed with them. Smoking cessation programs are available throughout the United States from the American Lung Association, the American Cancer Society, and the Seventh-Day Adventist Church. The American Heart Association also offers a self-help program. Many national and local commercial programs are also available. Developing a comfortable referral relationship with programs in your area can improve the care you provide for your smoking patients.

REFERENCES

1. Encyclopedia Britannica, Chicago:Encyclopedia Britannica Inc., 45th ed., 1978.
2. Jones S. Provision of Public Health Services. In Norwalk, CT:Appleton & Lange, Maxcy-Rosenan Public Health and Prevention Medicine. 11th ed., Last JM, ed., 1980, p. 1619.
3. U.S. Public Health Service: Smoking and Health. Report of the Advisory Committee to the Surgeon General of the Public Health Service. Washington, D.C.; Publication N:1103, 1964.
4. Royal College of Physicians: Smoking and Health. London, Pitman Medical, 1962.
5. Royal College of Physicians: Smoking and Health. London, Pitman Medical, 1977.
6. World Health Organization: Smoking and its effects on Health. Report of WHO Expert Committee, N:568, Geneva, 1975.
7. Surgeon General's Report: PHS Publication N:79-50066. Washington D.C., 1979.
8. American Heart Association. 2001 Heart and Stroke Statistical Update. Dallas, Texas: American Heart Association, 2000.
9. The Health Consequences of Smoking: Cardiovascular Disease. A report of the Surgeon General: U.S. Gov't Printing office, 1983.
10. Reducing the Health Consequences of Smoking: 25 years of progress. A report of the Surgeon General; CDC, Office on Smoking and Health, Rockville, Md., 1989.
11. Gottlieb AM, Sachs DPL, Newman BR. Smoking Cessation. ACSM's Resource Manual for Guidelines for Exercise Testing and Prescription, 2nd ed. Philadelphia: Lea and Gebrger, 1993, pp. 483-488.
12. Becker DM. Clinical Approaches to Cardiovascular Risk factors: Smoking. Primer in Preventive Cardiology. American Heart Association, 1994, pp.143-157.
13. Zimmerman M,Mc Geachie J. The effect of nicotine on aortic endothelium: A quantitative ultrastructure study. *Atherosclerosis* 1987; 63:33-41.
14. Davis JW, Shelton L, Hartman CR, Eioerberg DA, Ruttinger HA. Smoking-induced changes in endothelium and platelets are not affected by hydroxyethylrutosides. *Br J Exp Pathol* 1986; 67:765-771.
15. Hammond EC, Garginkel L, Seidman H, Lew EA. "Tar" and nicotine content of smoke in relation to death rates. Proceedings of the Conference on the origins of human cancer at Cold Spring Harbor Laboratory, New York, Sept. 14, 1976.
16. Johnason J, Ringquist I. Factors of prognastic importance for subsequent rest pain in patients with intermittent claudication. *Act Med Scand* 1985; 218:27-33.

17. Glantz SA, Parmley WW. Passive smoking and heart disease: epidemiology, physiology and biochemistry. *Circulation* 199; 83:1–12.
18. Steenland K. Passive smoking and the risk of heart disease. *JAMA* 1992; 267:94–99.
19. Helsing KJ, Sandler DP, Constock GW, Chee E. Heart disease mortality in non-smokers living with smokers. *Am J Epidemiol* 1988; 127:915–922.
20. Shinton R, Beeven G. Meta-analysis of relation between smoking and stroke. *Br Med J* 1989; 298:789–794.
21. Criqui MH, Browner D, Fromek A, Klauber Mr, Coughlin SS, Barrett-Connor E, Gabriel S. Peripheral arterial disease in large vessels in epidemiologically district from small vessel disease. An analysis of risk factors. *Am J Epidemiol* 1989; 129: 1110–1119.
22. Vogel JA, Rock PB, Jones BH, Havenith G. Environmental considerations in exercise testing and training. ACSM's Resource Manual for Guidelines for Exercise Testing and Prescriptions, 2nd ed. Philadelphia:Lean and Gebiger, 1993, pp. 129–147.
23. Rival J, Riddle JM, Stein PD. Effects of chronic smoking on platelet function. *Thromb Res* 1987; 45:75–85.
24. Meade TW, Imeson J, Stirling Y. Effects of changes in smoking and other characteristics on clotting factors and the risk of ischemic heart disease. *Lancet* 1987; 2:986–988.
25. Feid LP, Moore RD, Pearson TA. Long-term effect of cigarette smoking and moderate alcohol consumption on coronary artery diameter. Mechanisms of coronary artery disease independent of atherosclerosis or thromboses? *Am J Med* 1986; 80:37–44.
26. Ernst E, Matrai A. Abstinence from chronic cigarette smoking normalizes blood rheology. *Atherosclerosis* 1987; 64:75–76.
27. Stampfer MJ, Henderson CH, Manson JE, et al. Vitamin E consumption and the risk of coronary disease in women. *N Engl J Med* 1993; 328:1444–1449.
28. Rimun EB, Stampfer MJ, Ascherio A, et al. Vitamin E consumption and the risk of coronary heart disease in men. *N Engl J Med* 1993; 328:1450–1456.
29. Enstrom JE, Kanim LE, Klein MA. Vitamin C intake and mortality among a sample of the United States population. *Epidemiology* 1992; 3:194–202.
30. Fortmann SP, Haskell WL, Williams PT. Changes in plasma high density lipoprotein cholesterol after changes in cigarette use. *Am J Epidemiol* 1986; 124:706–710.
31. Gaziano JM, Manson JE, Ridker PM, et al. Beta carotene therapy for chronic stable angina. *Circulation* 1990; 82:111–201.
32. Mehra MR, Lavie CJ, Ventura HO, Milani RV. Prevention of atherosclerosis. The potential role of antioxidants. *Postgrad Med* 1995; 98:175–184.
33. Wilhelmsen L, Suardsudd K, Korsan-Bengsten K, Larsson B, Welvin L, Tibblin G. Fibrinogen as a risk factor for stroke and myocardial infarction. *N Engl J Med* 1984; 311:501–505.
34. Dotevall A, Kutti J, Teger-Nilsson A, Wadenui H, Wilhelmsen L. Platelet reactivity, fibrinogen and smoking. *Eur J Haematol* 1987; 38:55–59.
35. Cooke JP, Ma AO. Medical therapy of peripheral arterial occlusive disease. *Surg C North America* 1995; 75:569–579.
36. Gertler JP, Headly A, L'Italien G. Claudication in the setting of plethysmographic criteria for resting ischemia. *Is Surg* 1993; 7:249–253.
37. Hughson WG, Mann JI, Tibbs DJ, et al. Intermittent claudication. Factors determining outcome. *Brit Med J* 1978; 1:1377–1379.
38. Cronenwett JL, Warner KG, Zelenock GB, et al. Intermittent claudication. Current results of nonoperative management. *Arch Surg* 1984; 119:430–436.
39. Hughson WG, Mann JI, Garrod A. Intermittent claudication. Prevalence and risk factors. *Brit Med J* 1978; 1:137.

40. Klein LW. Cigarette smoking, atherosclerosis and the coronary hemodynamic response. A unifying hypothesis. *J Am Col Cardiol* 1984; 4:972-974.
41. Martin JL, Wilson JR, Ferraro N, Laskey WK, Kleaveland JP, Hirshfield JW Jr. Acute coronary vasoconstrictive effects of cigarette smoking in coronary heart disease. *Am J Cardiol* 1984; 54:56-60.
42. Caralis DG, Deligonul U, Kern MJ, Cohen JD. Smoking is a risk factor for coronary spasm in young women. *Circulation* 1992; 85:905-909.
43. Benowitz HL. Pharmacologic aspects of Cigarette smoking and nicotine addiction. *N Engl J Med* 1988; 319:1318-1330.
44. Kuhn FE, Mohler ER, Satler LF, Reagan K, Lu DY, Rackley CE. Effects of high-density lipoprotein on acetylcholine-induced coronary vaso-reactivity. *Am J Cardiol* 1991; 86: 1425-1430.
45. Feisbman WH, Sonnenblick EH. Beta-adrenergic blocking drugs. Hurst: The Heart 8th ed., Schlant R.C. and Alexander R.W., ed. Mc Graw-Hill Inc., 1994, pp. 1271-1290.
46. Klein LW, Ambrose J, Pichard A, Holt J, Corlin R, Teicholz E. Acute coronary Remodynamic response to cigarette smoking in patient with coronary artery disease. *J Am Coll Cardiol* 1984; 3:879-886.
47. Hartz AJ, Anderson AJ, Brooks HL, Manley JC, Parent GT, Barboriak JJ. The association of smoking with cardiomyopathy. *N Engl J Med* 1984; 311:1201-69-81.
48. Celermajer DS, Adams MR, Clarkson P, Robinson J, Mc Credie R, Donald A, Deanfield JE. Passive smoking and impaired endothelium dependent arterial dilatation in healthy young adults. *N Engl J Med* 1996; 334:150-154.
49. Hammond KS, Sorensen G, Youngstrom R, Ockene JK. Occupational exposure to environmental tobacco smoke. *JAMA* 1995; 274:12, 956-960.
50. Anderson R, Theron AJ, Richards GA, Myer MS, van Rensburg AJ. Passive smoking by humans sensitized circulating neutrophils. *Am Rev Resp Dis* 1991; 144: 570-574.
51. Kannel WB, D'Agostino RB, Belanger AJ. Fibrinogen, cigarette smoking and risk to cardiovascular disease. Insights from the Framingham Study. *Am Heart J* 1987; 113:1006-1010.
52. Hermanson B, Omenn GS, Kramal RA, Gersh BJ. Beneficial six-year outcome of smoking cession in older men and women with coronary artery disease. Results from the CASS study. *N Engl J Med* 1988; 319:1365-1369.
53. Rosenberg L, Kaufman DW, Helmrich SP, Shapiro S. The risk of myocardial infarction after quitting smoking in men under 55 years of age. *N Engl J Med* 1985; 313:1511-1514.
54. Lepantalo M, Lassila R. Smoking and occlusive peripheral arterial disease. Clinical review. *Eur J Surg* 1991; 157:83-87.
55. Krupski WC, Rapp JH. Smoking and atherosclerosis. *Persp Vase Surg* 1989; 1: 103-134.
56. Krikorian RK, Vacek JL. Peripheral arterial disease. *Postgr Med* 1995; 97:109-119.
57. Michael C, Fiore MC, Bailey WC, Cohen SJ, et al. Treating Tobacco Use and Dependence. U.S. Public Health Service, June 2000.
58. Shopland DR, Burns DM, Cohen SJ, Kottke TE, Gritz ER, eds. Tobacco and the Clinician: Intervention for Medical and Dental Practice. U.S. Dept. of Health and Human Services, Bethesda, MD, 1994.
59. Aronow WS. Book review. *Ann Int Med* 1994; 121:551.
60. Ockene JK, Kristeller J, Goldberg R, et al. Increasing the efficacy of physician-delivered smoking interventions: a randomized clinical trial. *J Gen Inter Med* 1991;6:1-8.

4

Peripheral Arterial Disease and Diabetes

George L. Bakris, MD, FACP, FAHA, FASN

CONTENTS

INTRODUCTION
ANATOMIC DISTRIBUTION OF DISEASE
RISK FACTORS
MORTALITY
CONCLUSION
REFERENCES

INTRODUCTION

The incidence of type 2 (noninsulin-dependent) diabetes mellitus continues to increase in the United States (1). Consequently, the associated morbid and mortal events from the associated microvascular and macrovascular complications of this disease have also risen (1). The preponderance of research toward the understanding of vascular disease in diabetes has been directed toward the delineation of end organ injury from microvascular disease. Consequently, the focus on macrovascular peripheral vascular disease has been relatively ignored. However, several studies have elucidated both the incidence and prevalence of peripheral vascular disease associated with both type 1 (insulin-dependent) and type 2 diabetes mellitus. In general, these studies have found that the duration of diabetes is perhaps the best correlate to predict the development of coronary artery and renal disease, as well as other associated end organ injuries that have not consistently correlated with the development of peripheral vascular disease.

From: *Clinical Hypertension and Vascular Diseases: Lower Extremity Arterial Disease*
Edited by: D. G. Caralis and G. L. Bakris © Humana Press Inc., Totowa, NJ

This chapter will review the available studies that report the incidence and prevalence of peripheral vascular disease in both type 1 and type 2 diabetic patients. It will focus not only on risk factors associated with the development of peripheral arterial disease, but also touch on pathophysiologic changes that may help to account for some epidemiologic trends. Lastly, it will highlight differences between diabetic and nondiabetic subjects concerning localization of disease and its association with mortality and limb loss.

ANATOMIC DISTRIBUTION OF DISEASE

Prospective studies have demonstrated that peripheral arterial disease associated with diabetes predominately affects the more distal circulation when compared to nondiabetic subjects with atherosclerotic disease. Specifically, the anterior and posterior tibial and peroneal arteries are affected to a greater extent than the femoral or iliac arteries in diabetics (2–4). Abbott et al. (2) reviewed the Framingham data base for the relationship between diabetes and development of peripheral arterial disease in the carotid and femoral circulations. They evaluated 20 years of follow-up data from the Framingham Study involving approximately 1200 men and 1600 women. They demonstrated that the incidence of carotid bruits and nonpalpable pedal pulses increased with age. However, in both diabetic men and women there was an increased risk for peripheral arterial disease that increased across all age groups. In addition, they noted that women without diabetes had a twofold excess in femoral bruits and nonpalpable pedal pulses compared to women without diabetes. Diabetic men also had approximately a twofold greater risk of carotid bruits when compared to nondiabetic men. Diabetes was also shown to be an important risk factor for the development of intermittent claudication in this study. Those who had both diabetes and peripheral arterial disease were at the highest risk for development of cardiovascular events. Moreover, presence of diabetes resulted in a worse prognosis for subsequent cardiovascular outcomes in the Framingham study (2–4). This group has a twofold excess in coronary heart disease and stroke, as well as heart failure. Lastly, presence of a femoral bruit doubled the risk of coronary disease in diabetic men in this study.

In a separate study by Witteman et al. (5), the presence of aortic calcified plaques on routine chest X-ray correlated with a twofold increased risk of cardiovascular death in men and women younger than age 65. A similar relative risk was noted for the development of coronary artery disease, stroke, and intermittent claudication among middle-age women. Lastly, the risk of sudden coronary death in men with calcified

aortic plaques in the thoracic aorta was sevenfold higher at age 35 compared to age 70, where no excess risk was noted. Therefore, radiographic abnormalities in the peripheral vasculature among younger individuals clearly correlates with the presence of accelerated cardiovascular disease.

As previously noted, atherosclerotic changes associated with diabetes have a similar prevalence in the femoral arteries, but have a much higher prevalence in the tibial and peroneal arteries (6). The reasons for this difference in location and extent of involvement in diabetic patients are not known. This involvement of the more distal and smaller vessels, however, correlates with a much higher incidence of amputations seen in the diabetic population when compared to the nondiabetic population with peripheral occlusive disease. In a 12-year follow-up study in 84 Pima Indians with diabetes, it was noted that the incidence of amputations increased with age (7). Moreover, these investigations noted that the death rate was greater among diabetic amputees than in nonamputees. These observations confirm other investigations that report similar increases in mortality among amputees (8,9).

These related studies clearly show that diabetes is associated with a more distal distribution of peripheral vascular disease when compared to nondiabetic atherosclerotic disease. While the mechanisms to explain this varied distribution are not known, it does support the clinical contention that diabetes will have more distal disease and should always have assessment of their peripheral vasculature if arterial disease is suspected.

RISK FACTORS

Many risk factors have been associated with the development of peripheral vascular disease in the diabetic patient. These are summarized in Table 1. These risk factors will each be discussed to its relative importance and contribution to the development and acceleration of pre-existing peripheral arterial disease. The prevalence of lower extremity arterial occlusive disease by noninvasive methods was examined by Beach et al. (10). They found that most risk factors including smoking history, duration of diabetes, reduction in high-density lipoprotein (HDL) cholesterol, total cholesterol elevations, and systolic blood pressure elevations correlated with the progression of pre-existing lower extremity arterial lesions among diabetic patients. These findings confirm previous investigations by this group that document an association between smoking and lipid abnormalities in contributing to the development of peripheral arterial disease (11,12). Moreover, it is important to

Table 1
Risk Factors for Accelerated Development
of Peripheral Artery Disease in Diabetic Subjects

Smoking
Elevated systolic blood pressure
Low HDL-cholesterol
Family history of peripheral arterial disease

Note in most studies, diabetes itself is associated with a much higher prevalence of peripheral artery disease compared to nondiabetic populations.

note that lower extremity occlusive disease is 20 times more likely to occur in type 2 diabetics than in age- and sex-matched control subjects (13). Although the histological changes of atherosclerosis in the diabetic is similar to the nondiabetic, the location and extent of involvement is different.

In a study of diabetic Pima Indians, Nelson et al. (7) identified risk factors associated with a high probability for limb amputation among diabetic individuals. These included: presence of diabetic retinopathy, nephropathy, hypertension, absent patellar tendon reflexes, and presence of medial arterial calcification. However, no single risk factor was identified as being relatively more important than another.

The most significant risk factor that has consistently been shown to aggravate pre-existing peripheral arterial disease in diabetics is smoking. In a study by Fowkes et al. (14), more than 1500 men and women between the ages of 55 and 74 years demonstrated that the only risk factor consistently associated with an increased risk of peripheral arterial disease was smoking. Moreover, smoking increased the risk for development of peripheral arterial disease in diabetics more than it did for development of heart disease. The aim of this study was to learn if certain risk factors in the general population are more strongly related to peripheral arterial disease than ischemic heart disease. Multiple regression analyses of various risk factors for the development of peripheral arterial disease was performed in both diabetic and nondiabetic and sex matched controls. These patients were obtained from ten general in Edinburgh, Scotland. The analyses showed an association between the development of peripheral arterial disease and diabetes, systolic blood pressure and serum cholesterol. This study also displayed an inverse association with the development of peripheral arterial disease and HDL-cholesterol as well as elevated triglycerides. Interestingly, diabetes alone was not a strong risk factor for development of peripheral arterial disease. In

another study by Beach (12), the prevalence of atherosclerotic peripheral vascular disease among diabetics was evaluated in 141 type 1 and 289 type 2 diabetic subjects and compared to 64 age matched controls. The prevalence of peripheral arterial disease among type 1 diabetics was 18% and in the older type 2 diabetes, 41%. The prevalence increased at 7.5% per decade in smokers. Thus, concomitant risk factors superimposed on diabetes are associated with an accentuated progression of peripheral arterial disease.

MORTALITY

Clearly, diabetics who have peripheral arterial disease have higher mortality rates than those who do not have arterial disease. A recent study by Vogt et al. (15) evaluated the relationship between peripheral arterial disease and mortality in a population of close to 2000 individuals over a 13-year period. All patients 50 years of age and older with no history of lower extremity surgery were evaluated for the presence of peripheral arterial disease. Analysis of the data stratified by populations and comorbid conditions showed that a low ankle-brachial index is an independent predictor of all causes of mortality in both men and women with peripheral arterial disease. This increase is a relative risk and is unchanged after exclusions of all patients with a clinical history of cardiovascular disease or diabetes. Thus, a low ankle-brachial index is an important measurement to obtain to assess the risk of mortality among those who smoke and have either angina or diabetes.

It is important to note that this increased predisposition for the development of peripheral vascular disease among diabetic patients is not true in patients who have simple glucose intolerance. Other studies have investigated the incidence in prevalence of peripheral vascular disease among patients with glucose intolerance, but not frank diabetes (16–17). In all cases, the incidence of peripheral arterial disease was no different among those who have glucose intolerance compared to age-matched controls. In the Casteldaccia study (18) that involved 102 healthy volunteers and 102 predominately male patients with peripheral arterial disease, factors such as arterial hypertension, hypercholesteremia, hypertriglyceridemia, smoking habits, and hyperglycemia were correlated with the incidence of peripheral arterial disease. This study showed that smoking and hypercholesterolemia were the most important risk factors for the development of peripheral arterial disease. Moreover, this and other studies point to the fact that in diabetic patients the diabetes *per se* may not be as important in the development of peripheral arterial disease as the increased serum cholesterol level, which generally portends this

disease process in nondiabetic subjects (18–20). In a study by Migdalis et al. (21,22) type 2 diabetic patients and 93 age- and sex-matched controls further supports this relationship. Subjects in this study were evaluated for risk factors associated with the development of peripheral vascular disease. Hypercholesterolemia was associated with the development of peripheral arterial disease, however, smoking was not significantly correlated with accenuated disease. Interestingly, diabetes itself clearly increased the risk for development of peripheral arterial disease. This reinforces the concept that hypercholesterolemia is an important parameter to monitor in order to help reduce progression of peripheral arterial disease in high-risk populations.

CONCLUSION

These studies all demonstrate unequivocally that hypercholesterolemia, especially in a diabetic individual, predisposes to acceleration of peripheral arterial disease. Smoking in these individuals will accelerate this process (22). Lastly, presence of systolic hypertension while contributing to the development of peripheral arterial disease, in most studies has not been shown to markedly accelerate its development. Therefore, clinical studies focusing on the mechanism of arterial wall injury from low-density lipoproteins as well as growth factor homeostasis of vessel injury repair, need to be performed in high-risk individuals so that the progression of this process can be attenuated.

REFERENCES

1. Geiss LS, Herman WH, Goldschmid MG, et al. Surveillance for diabetes mellitus-United States. *MMWR* 1993; 42:1–20.
2. Abbott RD, Brand FN, Kannel WB. Epidemiology of some peripheral arterial findings in diabetic men and women: experiences from the Framingham Study. *Am J Med* 1990; 88:376–381.
3. Brand FN, Abbott RD, Kannel WB. Diabetes, intermittent claudication, and the risk of cardiovascular events: The Framingham Study. *Diabetes* 1989; 38:504–509.
4. Janka HU, Standl E, Mehnert H. Peripheral vascular disease in diabetes mellitus and its relation to cardiovascular risk factors: screening with Doppler ultrasonic technique. *Diabetes Care* 1980; 3:207–213.
5. Witteman JC, Kannel WB, Wolf PA, et al. Aortic calcified plaques and cardiovascular disease (The Framingham Study). *Am J Cardio* 1990; 66:1060–1064.
6. West KM. *Epidemiology of Diabetes and its Vascular Lesions*. New York: Elsevier North-Holland, 1978.
7. Nelson RG, Gohdes DM, Everhart JE, et al. Lower extremity amputations in NIDDM; twelve year follow-up study in Pima Indians. *Diabetes Care* 1988; 11:8–16.
8. Jarrett RJ, Keen H, Chakrabarti R. Diabetes, hyperglycemia, and arterial disease. In: Keen H, Jarrett RJ, eds. *Complications of Diabetes*. 2nd ed. London: Edward Arnold, 1982, pp. 179–204.

9. Howard BV, Welty TK, Fabsitz RR, et al. Risk factors for coronary heart disease in diabetic and nondiabetic Native Americans. The Strong Heart Study. *Diabetes* 1992; 41: 4–11.
10. Beach KW, Bedford GR, Bergeling RO, et al. Progression of lower extremity arterial of exclusive disease in type II diabetes mellitus. *Diabetes Care* 1988; 11:464–472.
11. Beach KW, Strandness DE Jr. Arteriosclerosis, obliterans and associated risk factors that the insulin dependent and non-insulin dependent diabetes. *Diabetes* 1980; 29:882–888.
12. Beach KW, Brunzell JD, Strandness DE. Prevalence of severe arteriosclerosis obliterans in patients with diabetes mellitus. *Arteriosclerosis* 1982; 2:275–280.
13. Beach KW, Brunzell JD, Conquest LL, Strandness DE. The correlation of arteriosclerosis obliterans with lipoproteins in insulin-dependent and non-insulin dependent diabetes. *Diabetes* 1979; 28:836–840.
14. Fowkes FGR, Houslew E, Riemers MA, et al. Smoking, lipids, glucose intolerance and blood pressure as risk factors for peripheral atherosclerosis compared with ischemic disease in the Edinburgh Artery Study. *Am J Epidemiol* 1992; 135:331–340.
15. Vogt MT, McKenna M, Wolfson SK, Kuller LH. The relationship between ankle brachial index, other atherosclerotic disease, diabetes, smoking and mortality in older men and women. *Atherosclerosis* 1993; 101:191–202.
16. Yudkin JS, Forrest RD, Jackson CA. Misclassification of diabetic subjects may account for the increased vascular risk of impaired glucose tolerance: The Inslington Diabetes Survey. *Diabetes Res Clin Pract* 1991; 13:1–13.
17. Fujimoto WY, Leonetti DL, Bergstrom RW, Kinyoun JL, Stolov WC, Wahl PW. Glucose intolerance and diabetic complications among Japanese-American Women. *Diabetes Res Clin Pract* 1991; 13:119–129.
18. Novo S, Avellon G, Di Garbo V, et al. Prevalence of risk factors in patients with peripheral arterial disease. A clinical and epidemiological evaluation. *Int Angiol* 1992; 11:218–229.
19. Bhuripanyo P, Graisopa S, Suwanwatana C, et al. Vascular complications in noninsulin dependent diabetes mellitus (NIDDM) in Srinagarind Hospital, Khon Kaen. *J Med Asos Thai* 1992; 75:570–577.
20. Strandness DE Jr, Priest RE, Gibbons GE. Combined clinical and pathologic study of diabetic and nondiabetic peripheral arterial disease. *Diabetes* 1964; 13:366–372.
21. Migdalis IN, Kourti A, Zachariadis D, Voudouris G, Samartziz M. Peripheral vascular disease in newly diagnosed non-insulin-dependent diabetic. *Int Angiol* 1992; 11:230–232.
22. Levy LA. Smoking and peripheral vascular disease. *Podiatric Medical Update Clin Podiatr Med Surg* 1992; 9:165–171.

5

Hyperlipidemia in Peripheral Arterial Disease

*Ambika Babu, MD,
C. R. Kannan, MD,
and Theodore Mazzone, MD*

CONTENTS

INTRODUCTION
PATHOGENESIS OF ATHEROSCLEROSIS
ATHEROSCLEROSIS, DYSLIPIDEMIA, AND PERIPHERAL ARTERIAL DISEASE
INTERVENTIONAL TRIALS IN ATHEROSCLEROSIS
STATINS AND ATHEROSCLEROSIS
FIBRATES AND ATHEROSCLEROSIS
NIACIN AND ATHEROSCLEROSIS
LIPID LOWERING IN PERIPHERAL ARTERIAL DISEASE
CONCLUSIONS
REFERENCES

INTRODUCTION

Peripheral arterial disease (PAD) is a common manifestation of atherosclerosis affecting 18 to 20% of the population over age 75 (1,2). By the late fifth decade almost 8% demonstrate significant asymptomatic disease on noninvasive testing, whereas 5% have symptoms of intermittent claudication, which is a major manifestation (3). This is caused by muscle ischemia secondary to inadequate blood flow that is unable to meet oxygen demands during exercise. Intermittent claudication can lead to moderate to severe impairment in the patient's walking ability,

From: *Clinical Hypertension and Vascular Diseases: Lower Extremity Arterial Disease*
Edited by: D. G. Caralis and G. L. Bakris © Humana Press Inc., Totowa, NJ

and in turn can lead to disability if the patient is unable to meet the activities of daily living or those of their occupation.

PATHOGENESIS OF ATHEROSCLEROSIS

Atherosclerosis is a multifactorial disorder primarily affecting the large arteries of the carotid, coronary, and femoral beds. Clinical symptoms of atherosclerosis are manifested only late in its course. Atherosclerosis involves the deposition, modification, and cellular uptake of cholesterol derived from circulating lipoproteins (4). Vascular injury to the endothelium may be the initial event in the atherogenic process. Repetitive injury of the vessel wall leads to inflammation and vessel remodeling. Various factors including hyperlipidemia and diabetes cause injury to vessel wall. Injury promotes expression of chemo-attractants in the vessel wall that leads to recruitment of inflammatory cells. Inflammation is also associated with increased levels of acute phase reactants such as C-reactive protein, plasminogen activator inhibitor (PAI)-1, and tissue plasminogen. An increase in local PAI-1 level may result in impaired fibrinolysis. Retention and oxidation of low-density lipoprotein (LDL) in vessel wall underlies many features of the atherosclerotic plaque, including reduced availability of nitric oxide and endothelial dysfunction. Oxidized LDL also increases endothelial vasoconstriction and promotes expression of adhesion molecules, cytokines, growth factors, and endothelin. Endothelin is a thrombogenic factor that may promote plaque instability and thrombotic events.

Atherosclerotic lesions with a high lipid content and a thin fibrous capsule are most likely to lead to an acute clinical event. Inflammatory cells that accumulate within the plaque produce metallo-proteinases. These metallo-proteinases degrade the extracellular matrix of the fibrous cap of the plaque, predisposing to plaque rupture. Many of these factors can be modified by lipid-lowering therapy. Lipid lowering may stabilize the fibrofatty plaque by removing lipid, thickening the fibrous cap, and increasing the collagen content of the plaque, all of which leads to decreased incidence of spontaneous fissure and rupture. Lipid lowering can also result in improvement of endothelial function.

ATHEROSCLEROSIS, DYSLIPIDEMIA, AND PERIPHERAL ARTERIAL DISEASE

Factors associated with increased risk for intermittent claudication include smoking, hypertension, hyperlipidemia, and diabetes mellitus (5). Of these factors, hyperlipidemia has recently become the focus of intense study. A significant association between PAD, hyperlipidemia, and increased mortality secondary to coronary artery disease (CAD) and

cerebrovascular events has been noted. Fifty percent of patients who suffer from symptomatic PAD are dyslipidemic with total cholesterol >220 mg/dL and/or LDL >140 mg/dL (6). Conversely, in a study of patients with familial hypercholesterolemia (FH), 31% had hemodynamically significant PAD localized predominantly to the femoral-popliteal vessels and 30% had associated CAD. The incidence of PAD was highest (50%) in patients with FH and CAD, underscoring the diffuse nature of the atherosclerotic vascular disease (7). An increased incidence of femoral atherosclerosis has also been noted in asymptomatic patients with FH (8).

Compared to patients with CAD, patients with peripheral, carotid, and aortic atherosclerosis receive less attention to lipid risk factors (9,10). In one study of 299 patients with symptomatic PAD documented by angiography, only 27% had any lipid profiles done, and of these only 9% were receiving treatment for hypercholesterolemia (9). Physician recognition and management of hypercholesterolemia in patients with peripheral and carotid atherosclerosis undergoing vascular surgery was evaluated in 80 patients retrospectively (10). Of the 66% screened patients found to be hypercholesterolemic, only 24% received in-hospital management and only 13% received intervention at discharge. This underscores the need for education and greater awareness of surgeons and physicians involved in the management of patients with PAD.

INTERVENTION TRIALS IN ATHEROSCLEROSIS

Until the last decade, therapy for PAD was essentially limited to lifestyle recommendations such as cessation of smoking and regular physical exercise. Peripheral vasodilators were also utilized. Patients not responding to conservative treatment underwent invasive therapies such as surgery or angioplasty to achieve and maintain blood flow, as reflected by improvement in peripheral circulation and exercise capacity.

Recent advances have emphasized the importance of lipid lowering in the prevention of atherosclerosis and the management of its clinical manifestations. Stabilization and even reversal of the underlying atherosclerotic process can occur with lipid-lowering therapies. Multiple trials over the past decades have clearly shown that lowering elevated cholesterol levels reduces the progression of coronary atherosclerosis and lowers the incidence of acute coronary events. Extrapolating from these data, effective lipid reduction likely results in beneficial effects on the atherosclerotic process at other sites such as the carotid and femoral arteries, thereby reducing the need for invasive therapies.

Primary prevention trials such as Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) (11,12), West of Scotland Coronary Prevention Study Group (WOSCOPS) (13,14), and the

Helsinki Heart Study (15) have all demonstrated the benefit of lipid lowering using various hypolipidemic agents for prevention of initial cardiac events. Secondary prevention trials have unequivocally shown that lipid lowering therapy not only reduces acute coronary events and other clinical endpoints, but also results in angiographic improvement. These studies have used different classes of drugs (statins, fibrates, niacin, bile acid resins—alone and in combination) in both hyper- and normo-cholesterolemic patients with established CAD.

STATINS AND ATHEROSCLEROSIS

Statins have been used for secondary prevention of CAD with good results. Simvastatin has been evaluated in several studies including the Scandinavian Simvastatin Survival Study (4S) (16), the Simvastatin/Enalapril Coronary Atherosclerosis Trial (SCAT) (17), and the Multi-centre Anti-Atheroma Study (MAAS) (18). In addition to lowering LDL cholesterol levels, simvastatin has been shown to cause angiographic improvement in the coronary vessels, as well as slowing the progression of diffuse and focal atherosclerosis. In addition, the drug is believed to induce positive vascular remodeling, thereby reducing the occurrence of restenosis (19). The 4S study included 4444 patients with documented or symptomatic CAD. This was the first study to unequivocally demonstrate a reduction in the total CAD mortality (34% reduction in treated group with a 51% reduction in of coronary revascularization rate). Risk reduction was evident in multiple subgroups such as women, diabetics, and elderly patients (> 60 years of age). Similar results were seen in the SCAT study that evaluated normo-cholesterolemic patients with CAD, and the MAAS study that demonstrated less angiographic progression of atherosclerosis in the simvastatin treated group compared to the placebo group.

Lovastatin was used in the Canadian Coronary Atherosclerosis Intervention trial (CCAIT) (20–22) and the Monitored Atherosclerosis Repression Study (MARS) (23). The CCAIT study (20) was designed to evaluate whether lovastatin therapy retards the progression or facilitates the regression of coronary atherosclerosis as assessed by serial angiograms. This study concluded that the effect of lovastatin in preventing the formation of new coronary lesions might be more important than its effect on established lesions. Subgroup analysis in women and diabetics concurred with the main analysis. The MARS was the first trial that employed serial coronary angiograms to test the effects of a single drug therapy using lovastatin more than 2 years. The results showed that there was no significant difference in lesions <50% stenosed at baseline, but for lesions >50% stenosed at baseline there was regression.

The Cholesterol and Recurrent Events (CARE) trial (24), the Long Term Intervention with Pravastatin in Ischemic Disease (LIPID) study (25), and the Regression Growth Evaluation Statin study (REGRESS) (26–28) evaluated patients with established CAD given pravastatin. CARE reported a 24% reduction in the incidence of fatal and nonfatal coronary event in the treatment group, with a 23% reduction in the need for PTCA and a 31% reduction in the incidence of stroke. There were similar findings in the LIPID study that reported a 23% decrease in the incidence of combined fatal and nonfatal coronary events. In the REGRESS study, patients with established CAD treated with pravastatin demonstrated a significant event reduction, regardless of whether they had increased or normal cholesterol levels. These data imply that the non-LDL effects of the statins may also be important for the risk reduction with this class of drugs.

Atorvastatin, one of the most potent statins available, was used in the Atorvastatin Versus Revascularization Treatments (AVERT) study (29). This study randomized 341 patients with CAD to atorvastatin 80 mg/day vs angioplasty plus usual care. The mean LDL cholesterol in the atorvastatin group was 77 mg/dL compared to 119 mg/dL in the angioplasty group. Therapy with atorvastatin was associated with a significantly longer time to first ischemic event, which corresponded to a risk reduction of 36%.

The majority of late coronary events in patients post coronary artery bypass graft (CABG) relate to degeneration of saphenous vein grafts. Lipid lowering after coronary revascularization has been shown to prevent clinical events related to plaque instability, and inhibits progression of saphenous vein graft disease. In the Post Coronary Artery Bypass Graft trial, lovastatin was combined with cholestyramine to lower LDL levels to less than 85 mg/dL (30). Aggressive lowering of LDL showed significantly less progression of graft atherosclerosis compared with moderate lowering of LDL. Subgroup analysis was done to evaluate the treatment effects by age, gender, and selected cardiovascular risk factors such as diabetes, hypertension, high-density lipoprotein (HDL), and triglycerides (TG) levels (31). Aggressive lowering of LDL delayed progression of atherosclerosis irrespective of gender, age, and these risk factors for CAD.

FIBRATES AND ATHEROSCLEROSIS

Outcome studies employing the statins have conclusively shown that reduction of LDL translates into reduced clinical cardiovascular events. However, in patients with normal LDL or after LDL levels have been normalized, TG and HDL levels assume an important role in the progression of atherosclerosis. The importance of HDL-cholesterol as an inverse

risk factor for CAD is well known. Primary prevention trials such as the Helsinki Heart Study (15) using gemfibrozil therapy showed a 60% reduction in CAD events and a 34% reduction in cardiovascular deaths over a five year period in patients with low HDL levels.

Several secondary prevention trials using fibrates have evaluated the benefits of intervention in patients with normal to borderline total cholesterol and LDL levels with a low HDL level (<45 mg/dL) (32–35). The BECAIT trial using bezafibrate was the first major study to explore the effect of increasing HDL and/or decreasing TG on secondary prevention of CAD. This was a double-blinded placebo-controlled trial over 5 years in young males post myocardial infarction (MI). Effect on coronary atherosclerosis was studied by serial coronary angiograms. This trial showed that progression of coronary atherosclerosis was prevented, and coronary event rate was reduced primarily by lowering TG and increasing HDL without lowering serum LDL. The benefits were particularly marked on lesions of 20 to 50% stenosis at baseline.

The Veterans Affairs High-Density Lipoprotein Intervention Trial (VAHIT) study (36), was a double-blind randomized controlled trial in 2531 men with CAD whose major lipid abnormality was a low HDL-C of 40 mg/dL or less, treated with gemfibrozil during a period of 5.1 years. There was a 22% reduction in the primary end points, the risk of death from CAD or nonfatal MI, with an absolute risk reduction of 4%. The 22% reduction in major CAD was associated with a 6% increase in HDL-C, 33% decrease in TG, and no change in LDL-C levels.

These studies suggest the importance of TG-rich lipoprotein reduction and HDL raising for the retardation of atherosclerosis in mild to moderate lesions, and a role for fibric acid derivatives in secondary prevention. Analysis of data from Cholesterol Lowering Atherosclerosis Study (CLAS), the Program on the Surgical Control of Hyperlipidemias (POSCH), and MARS studies also provide evidence for the importance of TG rich lipoprotein in progression of CAD.

NIACIN AND ATHEROSCLEROSIS

Six major clinical trials have evaluated the effect of niacin on cardiovascular event reduction. The Coronary Drug Project (37), the largest of these trials used niacin as monotherapy for 6 years and reported significant reduction in recurrent MI, strokes, and transient ischemic attacks (TIAs). The CLAS (38) and Familial Atherosclerosis Treatment Study (FATS) studies (39) used niacin in combination with colestipol. CLAS was the first coronary angiographic trial to unequivocally demonstrate that there was regression of CAD with aggressive lipid-lowering therapy using this class of agents when compared to a placebo group. Treatment

benefits were seen at 2 and 4 years with an 18% regression of lesions at 4 years compared to 6.4% in the placebo group, and with reduction of clinical events by 20%. In native coronary arteries, both progression of existing lesions and development of new lesions was less at two and four years. In graft vessels, treatment with colestipol-niacin did not reduce the incidence of new closures, but it did reduce formation of new lesions both at 2 and 4 years emphasizing the need for early treatment of elevated lipids after CABG. The FATS, a randomized double-blinded coronary angiogram study over 2.5 years included subjects with LDL more than 125 mg/dL. A net regression of coronary disease with marked reduction in cardiovascular events was observed.

LIPID LOWERING IN PERIPHERAL ARTERIAL DISEASE

The studies of lipid lowering in PAD are heterogeneous in terms of the type of drugs used, inclusion criteria, and outcome measures. An advantage of lipid lowering in patients with intermittent claudication, but without symptomatic CAD is that such therapy would also be expected to reduce mortality from heart disease. In addition, it might improve local symptoms such as intermittent claudication, and reduce the need for reconstructive surgery. Several studies have validated the benefits of lipid lowering on femoral atherosclerosis. These studies included symptomatic patients with intermittent claudication, as well as asymptomatic patients with critical limb ischemia identified by abnormal ankle-brachial index (ABI) or peripheral angiogram. Disease progression was assessed by ultrasound, angiography, ABI, and exercise capacity evaluated by treadmill testing. Additional end points evaluated were fatal and nonfatal clinical events and subjective measures such as symptom improvement.

The Saint Thomas's Trial was the first randomized controlled trial evaluating the effect of lipid lowering therapy on the course of femoral atherosclerosis in hyperlipidemic patients with intermittent claudication (40). The patients were randomized to receive diet, cholestyramine, nicotinic acid, or clofibrate depending upon their lipoprotein phenotype. Total cholesterol (TC) decreased by 25%, LDL cholesterol by 28%, and TG by 45% following therapeutic intervention. Femoral atherosclerosis was studied by arteriography. In patients receiving lipid-lowering therapy, progression of atherosclerosis was reduced by 60% compared to the placebo group. The rate of increase in the cross-sectional area of the plaque in the treated group was one-third that of the placebo group. Change in edge irregularity was 2.5-fold greater in the placebo group, whereas twice as many arterial segments showed improvement in the therapy group.

The CLAS study (41) included 188 men with previous CABG and PAD, diagnosed by femoral angiograms, treated with colestipol and niacin for two years. The effect of therapy on femoral atherosclerosis was evaluated by estimating lumen abnormality measured by a computer-estimated atherosclerosis scale. Although a significant therapeutic benefit was observed in both femoral and coronary arteries, the effect was less marked on the femoral arteries. The HDL levels and the ratio of TC/HDL correlated with regression or progression of femoral atherosclerosis. Subjects who demonstrated regression of femoral atherosclerosis had higher HDL levels and a lower ratio of TC/HDL, than subjects who had no change in femoral atherosclerosis. Of particular interest, statistical significance was obtained for HDL levels only for femoral atherosclerosis and not for coronary atherosclerosis. A significant therapy effect was found in segments with moderately severe atherosclerosis and in proximal femoral segments. The POSCH trial (42) was a randomized single-blind controlled trial with a mean follow-up of 10 years. Patients with established CAD were assigned to diet only vs diet and partial ileal bypass surgery. LDL reduction of 38% was noted in the surgical group with an absolute risk reduction of 10%, and relative risk reduction of 35% for fatal and nonfatal CAD events. The POSCH trial also reported a reduction in symptoms of intermittent claudication in patients with PAD in the surgical group.

The ProbucoL Quantitative Regression Swedish Trial (43) (PQRST) was a 3-year study performed to investigate the effects of probucol, cholestyramine, and diet on atherosclerosis in the femoral arteries in patients with hypercholesterolemia, with or without clinical signs and symptoms of PAD. The primary endpoint was the change in atheroma volume of the femoral artery as estimated by annual measurements of angiograms of 20 cm segments of the femoral artery. Clinical events such as MI, silent MI, new onset angina, and other events were also noted. At the end of 3 years, the lumen volume of femoral arteries, cardiovascular event rates, and ABI were the same in both groups. It has been speculated that the benefit of LDL lowering by probucol was negated by the concomitant lowering of HDL level induced by this drug.

The 4S trial (44), in addition to CAD data, also reported the effects of therapy with simvastatin on noncoronary signs and symptoms during a median follow-up of 5.4 years. Patient assessment for these included a history of symptoms suggestive of intermittent claudication and a physical examination for carotid and femoral bruits that was done at baseline and followed annually. Risk of a new or worsening carotid bruit was substantially reduced by treatment, consistent with a reduction in cere-

brovascular events. Even though there was no statistically significant effect on femoral bruits, there was a 38% reduction in the incidence of new or worsening intermittent claudication.

In a nonrandomized trial Olsson et al. (45) evaluated the development of femoral atherosclerosis after one year of treatment with diet, nicotinic acid, and fenofibrate in 45 middle-aged men with asymptomatic hyperlipidemia. Disease progression was demonstrated in 24% of the treatment group compared to 40% in controls, whereas regression occurred in 29% and 0%, respectively.

CONCLUSIONS

Atherosclerosis is a life-long disease and measures to improve compromised blood flow by surgical methods or angioplasty is palliative. The main objective should be prevention of clinical disease by aggressive management of lipid abnormalities. The aim of treatment is to reduce LDL to <100 mg/dL, the same as for patients with prior CAD. Once lipid lowering is begun patients need regular follow-up to ascertain that the National Cholesterol Education Program (NCEP) targets are being maintained. Patients should be educated about the importance of lipid-lowering therapy to prevent further progression of atherosclerosis, especially after they undergo revascularization.

The Lipid-Treatment Assessment Project (L-TAP) (46) is a large epidemiological multicenter survey from a primary care setting to evaluate the percentage of dyslipidemic patients receiving lipid-lowering therapy and achieving LDL goals. Among the 4888 patients surveyed from five regions in the United States, 70% had 1 to >2 risk factors with no evidence of CAD, whereas 30% (1460 patients) had established CAD. Overall, only 38% achieved the NCEP specified LDL levels. Of particular concern was the fact that of the 1460 patients with established CAD, 82% did not reach their target LDL goal of <100 mg/dL. The reasons for not reaching therapeutic goals include patient compliance and lack of appropriate follow-up testing. In another study, up to 50% of patients on a lipid-lowering drug quit taking the drug after 1 year, with only 25% still taking their medications at the end of 2 years (47). Of patients taking the drugs, a minority were taking doses sufficient to lower LDL levels to target levels.

There is now a large body of evidence available indicating the important role of hyperlipidemia in the development of PAD. There is also convincing data to indicate that patients with PAD can greatly benefit from lipid-lowering therapy.

The current challenge is to find a way to utilize lipid-lowering strategies more effectively.

REFERENCES

1. Criqui MH, Fronek A, Barrett-Connor E, et al. The prevalence of peripheral arterial disease in a defined population. *Circulation* 1985; 71:510–515.
2. Biatt WR, Marshall JA, Baxter J, et al. Diagnostic methods for Peripheral arterial disease in the San Luis Valley Diabetes Study. *J Clin Epidemiol* 1990; 43:597–606.
3. Leng GC, Fowkes FGR. The epidemiology of peripheral arterial disease. *Vasc M Rev* 1993; 4:5–12.
4. Vogel RA. Cholesterol lowering and endothelial function. *Am J Med* 1999; 107: 479–487.
5. Tornwall ME, Virtamo J, Haukka JK, Arjmo A, Albanes D, Huttunen JK. Prospective study of diet, lifestyle, and intermittent claudication in male smokers. *Am J Epidemiol* 2000; 151:892–901.
6. Agishi T, Naganuma S, Nakasato S, Kitajima K, Ota K, Ban K, Nomura M. Treatment of arteriosclerotic obstruction by LDL adsorption. *Angiology* 1993; 44: 222–227.
7. Kroon AA, Ajubi N, van Asten WN, Stalenhoef AF. The prevalence of peripheral vascular disease in familial hypercholesterolaemia. *J Int Med* 1995; 23 8:451–459.
8. Ruhn G, Erikson U, Olsson AG. Prevalence of femoral atherosclerosis in asymptomatic men with hyperlipoproteinaemia. *J Int Med* 1989; 225:317–323.
9. Clark AL, Byrne JC, Nasser A, McGroarty E, Kennedy JA. Cholesterol in peripheral vascular disease—a suitable case for treatment? *QJM* 1999; 92:219–222.
10. Aspary KE, Holcroft JW, Amsterdam EA. Physician recognition of hypercholesterolemia in patients undergoing peripheral and carotid artery revascularization. *A J Preventive Med* 1995; 11:336–341.
11. Downs JR, Beere PA, Whitney E, Clearfield M, Weis S, Rothen J, Stein EA, Shapiro DR, Langendorfer A, Gotto AM Jr. Design & rationale of the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). *A J Cardiol* 1997; 80:287–293.
12. Gotto AM Jr, Whitney E, Stein EA, Shapiro DR, Clearfield M, Weis S, Jou JY, Langendorfer A, Beere PA, Watson DJ, Downs JR, de Cani JS. Relation between baseline and on-treatment lipid parameters and first acute major coronary events in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). *Circulation* 2000; 101:477–484.
13. Shepherd J, Cobbe SM, Ford I, et al. for the West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Eng J Med* 1995; 333:1301–1307.
14. West of Scotland Coronary Prevention Study Group. Baseline risk factors and their association with outcome in the West of Scotland Coronary Prevention Study. *Am J Cardiol* 1997; 79:756–762.
15. Frick MH, Elo O, Haapa K, et al. Helsinki Heart Study: Primary preventive trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors and incidence of coronary heart disease. *N Eng J Med* 1987; 317: 1237–1245.
16. The Scandinavian Simvastatin Survival Study group. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease. The Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994; 344: 1383–1389.

17. Teo KK, Burton JR, Buller CE, Plante S, Catellier D, Tymchak W, Dzavik V, Taylor D, Yokoyama S, Montague TJ. Long-term effects of cholesterol lowering and angiotensin-converting enzyme inhibition on coronary atherosclerosis: The Simvastatin/Enalapril Coronary Atherosclerosis Trial (SCAT). *Can J Cardiol* 1997; 13(6):591–599.
18. MAAS investigators. Effect of simvastatin on coronary atheroma: the Multicentre Anti-Atheroma Study (MAAS). *Lancet* 1994; 344:633–638.
19. Hagens T, Gussenhoven EJ, van Sambeek MR, Jukema JW, Kranendonk SE, Bom N. Effect of simvastatin on restenosis after percutaneous transluminal angioplasty of femoropopliteal arterial obstruction. *Am J Cardiol* 2000; 86: 774–776.
20. Waters D, Higginson L, Gladstone P, Kimball B, LeMay M, Bocuzzi SJ, et al. Atherosclerosis in coronary heart disease: effects of monotherapy with an HMGCoA reductase inhibitor on the progression of coronary atherosclerosis as assessed by serial quantitative arteriography the Canadian Coronary Atherosclerosis Intervention Trial. *Circulation* 1994; 89:959–968.
21. Waters D, Lesperance J, Gladstone P, Bocuzzi SJ, Cook T, Hudgin R, et al. Effects of cigarette smoking on the angiographic evolution of coronary atherosclerosis. A Canadian Coronary Atherosclerosis Intervention Trial (CCAIT) Substudy. CCAIT Study Group. *Circulation* 1996; 94:614–621.
22. Waters D, Higginson L, Gladstone P, Bocuzzi SJ, Cook T, Lesperance J. Effects of cholesterol lowering on the progression of coronary atherosclerosis in women. A Canadian Coronary Atherosclerosis Intervention Trial (CCAIT) substudy. *Circulation* 1995; 92:2404–2410.
23. Hodis HN, Mack WJ, LaBree L, Seizer RH, Liu C, Liu C, et al. Reduction in carotid arterial wall thickness using lovastatin and dietary therapy: a randomized controlled clinical trial. *Ann Int Med* 1996; 124:548–556.
24. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Eng J Med* 1996; 335:1001–1009.
25. The Long Term Intervention with Pravastatin in Ischemic Disease (LIPID) Study Group. Prevention of cardiovascular events and deaths with pravastatin in patients with coronary artery disease and a broad base of initial cholesterol levels. *N Engl J Med* 1998; 339:1349–1357.
26. Aengevaeren WR, Uijen GJ, Jukema JW, Brusckhe AV, van der Werf T. Functional evaluation of lipid-lowering therapy by pravastatin in the Regression Growth Evaluation Statin Study (REGRESS). *Circulation* 1997; 96:429–435.
27. Sacks FM, Pasternak RC, Gibson CM, Rosner B, Stone PH. Effect on coronary atherosclerosis of decrease in plasma cholesterol concentrations in normocholesterolaemic patients. Harvard Atherosclerosis Reversibility Project (HARP) Group. *Lancet* 1994; 344:1182–1186.
28. Tamura A, Mikuriya Y, Nasu M. Effect of pravastatin (10 mg/day) on progression of coronary atherosclerosis in patients with serum total cholesterol levels from 160 to 220 mg/dl and angiographically documented coronary artery disease. Coronary Artery Regression Study (CARS) Group. *Am J Cardiol* 1997; 79:893–896.
29. Pitt B, Waters D, Brown WV, et al. Aggressive lipid lowering therapy compared with angioplasty in stable coronary artery disease. Atorvastatin Versus Revascularization Treatments (AVERT). *N Eng J Med* 1999; 341:70–76.
30. The Post Coronary Artery Bypass Graft Trial Investigators. The effect of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagula-

- tion on obstructive changes in saphenous-vein coronary artery bypass grafts. *N Eng J Med* 1997; 336:153–162.
31. Campeau L, Hunninghake DB, Knatterud GL, White CW, Domanski M, Forman SA, et al. Aggressive cholesterol lowering delays saphenous vein graft atherosclerosis in women, the elderly, and patients with associated risk factors. NHLBI post coronary artery bypass graft clinical trial. Post CABG Trial Investigators. *Circulation* 1999; 99:3241–3247.
 32. Frick MH, Syvanne M, Nieminen MS, Kauma H, Majahalme S, Virtanen V, et al. Prevention of the angiographic progression of coronary and vein-graft atherosclerosis by gemfibrozil after coronary bypass surgery in men with low levels of HDL cholesterol. Lipid Coronary Angiography Trial (LOCAT) Study Group. *Circulation* 1997; 96:2137–2143.
 33. U. Goldbourt, D. Brunner, S. Behar, H. Reicher-Reiss, for the BIP Study Group. Baseline characteristics of patients participating in the Bezafibrate Infarction Prevention (BIP) Study. The BIP (Bezafibrate Infarction Prevention) Study Group. *Eur Heart J* 1998; 19:H42–H47.
 34. Ericsson CG. Results of the Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT) and an update on trials now in progress. *Eur Heart J* 1998; 19: H37–H41.
 35. Ericsson CG, Nilsson J, Grip L, Svane B, Hamsten A. Effect of bezafibrate treatment over five years on coronary plaques causing 20% to 50% diameter narrowing (The Bezafibrate Coronary Atherosclerosis Intervention Trial [BECAIT]). *Am J Cardiol* 1997; 80:1125–1129.
 36. Rubins HB, Robins SJ, Collins D, et al. for the VAHIT Study Group. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. *N Eng J Med* 1999; 341:410–418.
 37. The Coronary Drug Project Research Group (CDP). Clofibrate and niacin in coronary heart disease. *JAMA* 1975; 231:360–381.
 38. Blankenhorn DH, Nessim SA, Johnson RL, et al. Beneficial effects of combined colestipol niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. *JAMA* 1987; 257:3233–3240.
 39. Brown G, Albers JJ, Fisher LD, et al. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. *N Eng J Med* 1990; 323:289–298.
 40. Duffield RG, Lewis B, Miller NE, Jamieson CW. Treatment of hyperlipidemia retards progression of symptomatic femoral atherosclerosis. *Lancet* 1983; 2(8351): 639–642.
 41. Blankenhorn DH, Azen SP, Crawford DW, Nessim SA, et al. Effects of colestipol-niacin therapy on human femoral atherosclerosis. *Circulation* 1991; 83:438–447.
 42. Buchwald H, Varco RL, Marts JP, Long JM, Pitch LL, Campbell GS, et al. Effect of partial ileal bypass surgery on mortality and morbidity from coronary heart disease in patients with hypercholesterolemia. Report of the Program on the Surgical Control of Hyperlipidemias (POSCH). *N Eng J Med* 1990; 323:946–955.
 43. Walldius G, Erikson U, Olsson AG, Bergstrand L, Hadell K, Johansson J, et al. The effect of probucol on femoral atherosclerosis: the ProbucoL Quantitative Regression Swedish Trial (PQRST). *Am J Cardiol* 1994; 74:875–883.
 44. Pedersen TR, Kjekshus J, Pyorala K, et al. Effect of Simvastatin on Ischemic Signs and Symptoms in the Scandinavian Simvastatin Study Study. *Am J Cardiol* 1998; 81:333–335.

45. Olsson AG, Ruhn A, Erikson U. The effect of serum lipid regulation on the development of femoral atherosclerosis in hyperlipidaemia: a non-randomized controlled study. *J Int Med* 1990; 227:381–90.
46. Pearson TA, Laurora I, Chu H, Kafonek S. The lipid treatment assessment project (L-TAP): a multicenter survey to evaluate the percentages of dyslipidemic patients receiving lipid-lowering therapy and achieving low-density lipoprotein cholesterol goals. *Arch of Int Med* 2000; 160:459–467.
47. Roberts WC. The under used miracle drugs: the statin drugs are to atherosclerosis what penicillin was to infectious disease. *Am J Cardiol* 1996; 78:377–378.

6

Hypertension and Peripheral Vascular Disease

*Anjula Gandhi, MD, Jay Garg, MD,
and George L. Bakris, MD, FACP,
FAHA, FASN*

CONTENTS

INTRODUCTION
RISK FACTORS
CONCLUSIONS
REFERENCES

INTRODUCTION

The majority of deaths in western societies such as the United States are attributed in large part to arteriosclerosis, or hardening and thickening of the arterial wall (1). Underlying peripheral vascular disease as well as coronary artery and cerebrovascular disease is atherosclerosis, a disorder of larger arteries and one type of arteriosclerosis (1). Atherosclerosis is the leading cause of death in the general population in industrialized countries (1). It is well recognized that hypertension plays a major role in the pathogenesis of atherosclerotic vascular disease (2-11). This has important implications from a public health perspective because of the high prevalence of hypertension and its amenability to effective treatment.

The mechanism for the pathogenesis of atherosclerosis is generally considered separate from hypertension. Hypertension, however, accelerates the atherosclerotic process in large part as a result of increased shear stress on arterial walls. This increased shear stress stimulates a variety of proliferative growth factors, e.g., platelet-derived growth factor, endothelin, and others that ultimately enhance the atherosclerotic

From: *Clinical Hypertension and Vascular Diseases: Lower Extremity Arterial Disease*
Edited by: D. G. Caralis and G. L. Bakris © Humana Press Inc., Totowa, NJ

process. This process is exemplified by the Charcot-Bouchard aneurysms and fibrinoid arteriolar necrosis seen in hypertensives (5).

This chapter will focus on the epidemiology of peripheral vascular disease seen among hypertensive subjects. It will delineate both the incidence and prevalence of this disease, as well as elucidate risk factors for the development of peripheral vascular disease in hypertensive populations.

RISK FACTORS

The leading cause of occlusive arterial disease in the extremities in patients over the age of 40 years is atherosclerosis (12). Atherosclerosis of the peripheral arterial system is most commonly seen in elderly males; the peak incidence occurs in the sixth and seventh decades of life (12). The recognized risk factors for this important disease in the general population are outlined in Table 1. Risk factors include cigaret smoking, hypertension, hypercholesterolemia, hypertriglyceridemia, and diabetes as demonstrated in the landmark Framingham study (13). An additional risk factor may be the presence of an abnormal fibrinogen locus genotype (14). The sequelae of peripheral vascular disease occur approximately two to three times as frequently in hypertensives when compared to normotensives matched for age (5,6,11). Whereas hypertension alone is an independent risk factor for peripheral vascular disease, it frequently occurs in association with other powerful predictors for development of atherosclerosis that include diabetes, obesity, and adverse lipid profiles (4,6-9). Thus, hypertension may be viewed as a significant, multifaceted metabolic disturbance that has been termed *Syndrome X* (15). It is perhaps this tendency for association with other risk factors that makes it difficult to assess the contribution of hypertension alone to the development of peripheral vascular disease.

Surprisingly, no clinical trials have specifically addressed the contribution of hypertension to the development of peripheral arterial disease. Most of the data comes from multiple regression analysis of many parameters looking for correlations, or subgroup analysis of trials designed primarily to look at coronary artery disease. However, Kannel et al. (6) has shown that epidemiological data analyzed in this way accurately predicts disease risk in a variety of American population samples, and in elderly as well as young coronary candidates.

There has been an enormous amount of analysis and re-analysis of Framingham data in the literature. The incidence of hypertension in the Framingham cohort increased with age in men from 3.3% at ages 30-39 to 6.2% at ages 70-79, and in women from 1.5% at ages 30-39 to 8.6%

Table 1
Major Risk Factors for Accelerated Risk
of Peripheral Vascular Disease in Hypertensive Subjects

- Smoking
 - Diabetes
 - Hypercholesterolemia
 - Hypertriglyceridemia
-

at ages 70–79 (16). Stokes et al. (13) reviewed data from 30 years of follow-up of the original Framingham study cohort of 5070 men and women aged 30–62 years who were first examined during 1948–1952, and who were at that time free of cardiovascular disease. Multiple regression analysis revealed that blood pressure is a strong and consistent predictor for the development of coronary heart disease, stroke, transient ischemic attack, and congestive heart failure, as well as peripheral vascular disease. The authors note that risk factors related to hypertension like obesity and left ventricular hypertrophy (as demonstrated on electrocardiograms [ECGs]) were independent. Moreover, heart enlargement by X-ray radiography was the best predictor of congestive heart failure. Kannel et al. (6) reviewed the same database and noted that the risk of peripheral vascular disease and especially coronary disease associated with hypertension, hyperlipidemia, or diabetes varies widely depending on the level of associated risk factors. Habits, such as cigarette smoking or lack of exercise, can independently affect the risk associated with any of the atherogenic traits. Analysis of the Framingham data found that at a given level of total cholesterol, risk is greatly affected by the total/high-density lipoprotein (HDL) cholesterol ratio; low HDL values were associated with greater prevalence of peripheral vascular disease, especially in diabetics.

Further analysis of 50 years of Framingham research showed that hypertension is a powerful risk factor accounting for about 35% of atherosclerotic cardiovascular disease. Hypertension was shown to predispose powerfully to all of the major atherosclerotic cardiovascular events including coronary artery disease, stroke, peripheral arterial disease, and heart failure. An analysis of risk of cardiovascular events in subjects with hypertension in persons aged 35–64 years in a 36-year follow-up of the Framingham study showed that the age-adjusted biennial rate per 1000 for peripheral arterial disease was 10 for men and 7 for women. The age-adjusted risk ratio was 2.0 for men and 3.7 for women, and the excess risk per 1000 was 5.0 for both men and women (17).

Table 2
Logistic Regression Estimates and Odds Ratio
for Significant Risk Factors in the Intermittent Claudication

<i>Risk factor</i>	<i>Odds ratio (95% CI)</i>	<i>p</i>
Male sex	1.7 (1.3, 2.1)	.0001
Age (per 10 years)	1.5 (1.3, 1.6)	.0001
High normal blood pressure	1.3 (0.9, 1.8)	.1384
Stage 1 hypertension	1.5 (1.1, 2.0)	.0091
Stage 2 hypertension	2.2 (1.7, 3.0)	.0001
Diabetes	2.6 (2.0,3.4)	.0001
Cigaretts (per 10 cigarets)	.4 (1.3, 1.5)	.0001
Cholesterol (per 40 mg/dL)	1.2 (1.1, 1.3)	.0001
CHD	2.7 (2.2, 3.4)	.0001

Murabito et al. (18) used the 38-year follow-up data for the original cohort in the Framingham Heart study and developed an intermittent claudication (IC) risk profile. An individual's probability of developing IC was assessed by the presence of risk factors identified on routine physical examination and laboratory analysis performed at a physician's office. The results showed that during 38 years of follow-up, 381 persons (215 men and 166 women) developed IC. In contrast to subjects free of IC, those with IC were more likely to be male, older, have a higher mean cholesterol, have a higher prevalence of stage 2 or greater hypertension, be diabetic, have coronary heart disease, and smoke a greater number of cigarets per day. In the logistic regression model, male sex, age, and smoking were associated with an approximately 1.5-fold increased risk for IC. Diabetes and stage 2 hypertension conferred a greater than two-fold increased risk, and coronary heart disease nearly tripled the risk. Table 2 shows the logistic regression estimates and odds ratio for significant risk factors in the IC profile in subjects aged 45 to 84 (18).

In a review of studies describing target organ damage in African patients with essential hypertension, it was demonstrated that occlusive disease of the central and peripheral arteries is an important complication of essential hypertension. Although smoking, hypercholesterolaemia, and diabetes played an important role in the pathogenesis of central and peripheral vascular disease, this condition is more frequently seen in hypertensive than in normotensive patients (19).

Some studies have demonstrated the relationship between hypertension and peripheral vascular disease by looking at higher risk populations, e.g., the elderly. Ness et al. (20), in a retrospective analysis of older patients charts seen from January 1, 1998, through June 15, 1999, at an

academic, hospital-based geriatrics practice, have shown that hypertension was a significant independent risk factor for symptomatic peripheral arterial disease in the older men (odds ratio = 2.2) and women (odds ratio = 2.8). A total of 467 men (mean age 80 ± 8 years) and 1444 women (mean age 81 ± 8 years) were included in the study. In a larger study, Newman et al. (21) analyzed a subgroup of 1775 participants of the Systolic Hypertension in the Elderly Program (SHEP) to assess epidemiological correlates of peripheral vascular disease. The authors defined a patient as having peripheral arterial disease if the ankle–arm index was 0.9 in either leg. In this subgroup, the prevalence of peripheral vascular disease was 25% in white men, 38% in black men, 23% in white women, and 41% in black women. The authors found that even in the absence of risk factors such as smoking and diabetes, blacks had a higher prevalence of peripheral vascular disease than whites. Independent factors associated with the presence of peripheral vascular disease included age, black race, smoking, diabetes mellitus, history of myocardial infarction or angina, systolic hypertension, lower HDL cholesterol, and body mass index. However, the investigators also noted that although the prevalence of peripheral arterial disease was high in this study very few of the patients actually had symptoms of claudication. This would suggest that claudication is a very insensitive marker for peripheral vascular disease in this population.

As stated previously, peripheral vascular disease is not always symptomatic, but hypertension is still a significant risk factor for this type of disease. Hooi et al. (22) did a multiple logistic regression analysis of risk factors associated with the probability of asymptomatic and symptomatic peripheral arterial occlusive disease in a longitudinal study of 2327 subjects. The results showed that older age, smoking, hypertension, diabetes, hypercholesterolemia, and a sedentary lifestyle were the most important risk factors for asymptomatic peripheral arterial occlusive disease, whereas older age, smoking, hypertension, and diabetes were the most important predisposing factors for symptomatic peripheral arterial occlusive disease. Multiple logistic regression results showed hypertension was associated with the development of symptoms of IC (odds ratio = 1.5).

As is intuitive, hypertension is associated with established atherosclerotic disease. Multiple studies have shown that hypertension is present in these patients or in those known to be at high risk for atherosclerosis. Bull et al. (2) reviewed the cases of 232 patients receiving heart transplants at the University of Arizona at Tucson between 1979 and 1990. They found that accelerated coronary atherosclerosis occurred in 45 (19%) of the 232 patients, typically appearing within 2 years of trans-

plantation, whereas peripheral vascular disease appeared in 23 (10%) of the 232 patients usually within 3 years of transplantation. In those patients with peripheral vascular disease, 13 had occlusive disease, 9 had aneurysms, and 1 patient suffered a vertebral artery dissection. Accelerated coronary atherosclerosis afflicted 12 (52%) of the 23 patients affected by peripheral vascular disease ($p < 0.05$), and preceded the development of the peripheral vascular disease in all 12. The authors used regression analysis to ascertain risk factors predictive of the development of peripheral vascular disease after transplantation. The most powerful predictors for development of peripheral arterial disease were: (1) a pretransplant history of ischemic cardiomyopathy, and (2) posttransplant hypertension and hypertriglyceridemia ($p < 0.05$), with the presence of more than one risk factor increasing the probability of development of peripheral vascular disease. The authors suggest that aggressive medical management of hypertension and hyperlipidemia in this subpopulation may forestall or prevent the development of peripheral vascular disease after heart transplantation (2).

Lee et al. (7) retrospectively reviewed the cases of 110 patients with peripheral vascular disease who underwent amputation between 1987 and 1990 at the Hahnemann University Hospital in Philadelphia, PA. The purpose of their review was to evaluate the prevalence of diabetes and other common predisposing factors in amputation of the lower extremities. The combination of diabetes and hypertension was present in 40 of these patients (36%). The investigators found when either diabetes or hypertension was present in a patient, hypertension not diabetes was the more common dominant underlying medical condition in patients with amputations (32 hypertensive alone patients vs 10 diabetes-alone patients). This study supports the concept that hypertension plays an important role in the development of peripheral vascular disease.

Swartbol et al. (10) studied 450 consecutive patients with peripheral vascular disease to evaluate risk factors associated with renal artery stenosis. Of 221 patients who had peripheral arterial disease and a renal artery lesion detected by angiography, 44 were normotensive and 177 were hypertensive. The authors concluded that hypertension secondary to renal artery stenosis was significantly correlated with peripheral vascular disease. They also noted an association with age over 70 years, smoking history, and an abnormal baseline ECG.

Not all epidemiological studies, however, confirm hypertension as a consistent risk factor for the development of peripheral vascular disease. Fowkes et al. (4) designed a retrospective study to assess risk factors in the general population that might be more powerful for the prediction of the development of peripheral arterial disease rather than coronary artery

disease. These investigators assessed arterial disease in the lower limbs using the World Health Organization (WHO) questionnaire designed to assess IC, the ankle-brachial pressure index, and a reactive hyperemia test. They evaluated 1592 men and women aged 55–74 years that were selected randomly in 1988 from ten general medical practices in Edinburgh, Scotland. Multiple regression of risk factors on measures of peripheral arterial disease showed associations with diabetes mellitus (but not impaired glucose tolerance), systolic blood pressure, and serum cholesterol; an inverse association with high-density lipoprotein cholesterol was identified; and only a univariate association with triglycerides was seen. The only consistent finding that emerged from multiple logistic regressions of risk factors on six separate indicators of cardiovascular disease was that smoking increased the risk of peripheral arterial disease more than heart disease. The authors concluded that diabetes and hypertension are not stronger risk factors for peripheral vascular disease than coronary disease.

Additional studies by Novo et al. (8,9) studied the prevalence of arterial hypertension and other risk factors in patients suffering from peripheral arterial disease in two different populations: (1) the Trabia study ($n = 835$) and (2) the Casteldaccia study ($n = 723$). In the Trabia study, the investigators observed a significantly ($p < 0.01$) greater prevalence of arterial hypertension (51.9 vs 9.8%), hypercholesterolemia (48.2 vs 21.6%), hypertriglyceridemia (53.7 vs 26.1%), smoking (64.3 vs 44.2%), and hyperglycemia (26 vs 7.9%) in patients with peripheral vascular disease than in age and sex matched controls. However, in the Casteldaccia study the most important risk factors were smoking (64.28%), hypercholesterolemia (42.86%), and hypertriglyceridemia (35.71%) in males, and obesity (60%), hypercholesterolemia (30%), and diabetes (20%) in females. In this cohort, total cholesterol levels and smoking were significantly higher in patients with peripheral arterial disease than in the general population. The authors did not find a significant association of arterial hypertension with peripheral vascular disease in the Casteldaccia study.

CONCLUSIONS

These studies generally support the concept that hypertension accelerates development of peripheral vascular disease in certain populations. The presence of other risk factors such as hypercholesterolemia, smoking, diabetes, and male gender appear to markedly accentuate the effects of hypertension on development of this process. Thus, aggressive reduction in arterial pressure and reduction or elimination of other risk factors is clearly indicated in high-risk patients.

REFERENCES

1. El B. Atherosclerosis and other forms of arteriosclerosis. In: Wilson JD BE, Isselbacher KJ, ed. *Harrison's Principles of Internal Medicine*. New York: McGraw-Hill, Inc., 1991, p. 992.
2. Bull DA, Hunter GC, Copeland JG, et al. Peripheral vascular disease in heart transplant recipients. *J Vascu Surg* 1992; 16:546–553; discussion 553–554.
3. Chobanian AV. Vascular effects systemic hypertension. *Am J Cardiol* 1992; 69:3E–7E.
4. Fowkes FG, Housley E, Riemersma RA, et al. Smoking, lipids, glucose intolerance, and blood pressure as risk factors for peripheral atherosclerosis compared with ischemic heart disease in the Edinburgh Artery Study. *Am J Epidemiol* 1992; 135:331–340.
5. Kannel WB, Higgins M. Smoking and hypertension as predictors of cardiovascular risk in population studies. *J Hypertens Suppl* 1990; 8S3–8S8.
6. Kannel WB, Larson M. Long-term epidemiologic prediction of coronary disease. The Framingham experiences. *Cardiology* 1993; 82:137–152.
7. Lee CS, Sariojo J, Matsumoto T. Changing patterns in the predisposition for amputation of the lower extremities. *Am Surg* 1992; 58:474–477.
8. Novo S, Avellone G, Di Garbo V, et al. Prevalence of risk factors in patients with peripheral arterial disease. A clinical and epidemiological evaluation. *Int Angiol* 1992; 11:218–229.
9. Strano A, Novo S, Avellone G, et al. Hypertension and other risk factors in peripheral arterial disease. *Clin Exp Hypertens* 1993; 15:71–89.
10. Swartbol P, Thorvinger BO, Parsson H, Norgren L. Renal artery stenosis in patients with peripheral vascular disease and its correlation to hypertension. A retrospective study. *Int Angiol* 1992; 11:195–199.
11. WB K. Hypertension and the risk of cardiovascular disease. In: BM LjaB, ed. *Hypertension. Pathophysiology, Diagnosis, and Management*. Vol. 1. New York: Raven Press, 1990, p. 101.
12. VJ CmaD. Vascular diseases of the extremities. In: Wilson JD BE, Isselbacher KJ, ed. *Harrison's Principles of Internal Medicine*. New York: McGraw-Hill, Inc., 1991, pp.1018–1026.
13. Stokes J, erd, Kannel WB, Wolf PA, D'Agostino RB, Cupples LA. Blood pressure as a risk factor for cardiovascular disease. The Framingham Study—30 years of follow-up. *Hypertension* 1989; 13:113–118.
14. Fowkes FG, Connor JM, Smith FB, Wood J, Donnan PT, Lowe GD. Fibrinogen genotype and risk of peripheral atherosclerosis. *Lancet* 1992; 339:693–696.
15. Kubler W, Opherk D, Tillmanns H. Syndrome X: diagnostic criteria and long term prognosis. *Can J Cardiol* 1986; Suppl A:219A–220A.
16. Dannenberg AL, Garrison RJ, Kannel WB. Incidence of hypertension in the Farmingham Study. *Am J Public Health* 1988; 78:676–679.
17. Kannel WB. Fifty years of Farmingham Study contributions to understanding hypertension. *J Hum Hypertens* 2000; 14:83–90.
18. Murabito JM, D' Agostino RB, Silbershatz H, Wilson WF. Intermittent claudication. A risk profile from the Framingham Heart Study. *Circulation* 1997; 96:44–49.
19. Mensah GA, Barkey NL, Cooper RS. Spectrum of hypertensive target organ damage in Africa: a review of published studies. *J Hum Hypertens* 1994; 8:799–808.
20. Ness J, Aronow WS, Ahn C. Risk factors for symptomatic peripheral arterial disease in older persons in an academic hospital-based geriatrics practice. *J Am Geriatr Soc* 2000; 48:312–314.

21. Newman AB, Sutton-Tyrrell K, Kuller LH. Lower-extremity arterial disease in older hypertensive adults. *Arterioscler Thromb* 1993; 13:555–562.
22. Hooi JD, Kester AD, Stoffers HE, Overdijk MM, Van Ree JW, Knottnerus JA. Incidence of and risk factors for asymptomatic peripheral arterial occlusive disease: a longitudinal study. *Am J Epidemiol* 2001; 153:666–672.

7

Physical Inactivity is a Risk Factor for Lower Extremity Arterial Disease and Coronary Heart Disease

Dennis G. Caralis, MD, PhD, MPH, FAHA, FACC and Stamatis Dimitropoulos, MD

CONTENTS

INTRODUCTION
DOES ON-THE-JOB PHYSICAL ACTIVITY PROVIDE PROTECTION?
PHYSICAL INACTIVITY IS AN INDEPENDENT RISK FACTOR FOR THE DEVELOPMENT OF CARDIOVASCULAR DISEASE, CORONARY DISEASE, AND LOWER EXTREMITY ARTERIAL DISEASE
WHAT IS THE RELATION OF PHYSICAL FITNESS TO FUTURE CARDIOVASCULAR EVENTS OR TOTAL MORTALITY?
HIGHER LEVELS OF PHYSICAL FITNESS DELAY ALL-CAUSE MORTALITY AND CARDIOVASCULAR MORTALITY IN PARTICULAR
DOES MODERATE DAILY EXERCISE HAVE AN IMPACT ON SECONDARY PREVENTION OF CORONARY HEART DISEASE?
PROPOSED BIOLOGICAL MECHANISMS BY WHICH EXERCISE MAY CONTRIBUTE TO THE PRIMARY AND SECONDARY PREVENTION OF CORONARY HEART DISEASE
REFERENCES

From: *Clinical Hypertension and Vascular Diseases: Lower Extremity Arterial Disease*
Edited by: D. G. Caralis and G. L. Bakris © Humana Press Inc., Totowa, NJ

INTRODUCTION

Coronary arterial disease, carotid artery disease, and Lower Extremity Arterial Disease (LEAD) have many causes. Risk factors associated with these disease entities, which can be modified are: cigaret smoking, arterial hypertension, diabetes mellitus, various dislipidemias, i.e., hypertriglyceridemia in particular for LEAD, high low-density lipoprotein (LDL) cholesterol particularly for coronary artery disease, high lipoprotein(a) [Lp(a)], low high-density lipoprotein (HDL) cholesterol, obesity, homocysteinemia, elevated high sensitivity C-reactive protein (CRP), and physical inactivity (1–3). Significant progress has been made to lower the trend for cigaret smoking in the United States and other industrialized countries through educational programs for the public, reviews by the press, legislative action at all three levels of government (local, state, and federal), as well as landmark decisions by the judiciary. The pioneering work of the American Heart Association in initiating smoking cessation programs was closely followed by the American Lung Association, the American Cancer Society, the World Health Organization (4), and more recently by the European Union.

Not much progress has been made with regards to obesity and physical inactivity as risk factors for cardiovascular disease (CVD). Since 1970, obesity in the United States has become a public health problem and continues to grow. The concept that sedentary lifestyle may lead to an increase in prevalence of CVD, especially myocardial infarction (MI) and sudden cardiac death, has been recognized by cardiovascular physicians and all health care providers (5).

Data relating to the level of regular exercise and risk for all CVDs have been derived from a variety of sources, including annual patient studies, observational studies, prospective studies, and retrospective studies (6–9). The risk for CVD and LEAD in particular increases with sedentary lifestyle as opposed to a physically active lifestyle (10–12). No study has been executed so far that provides biological evidence of the cause or causes, biochemical link or links, between exercise status and cardiovascular morbidity and mortality or the specific pathophysiology of physical inactivity. The basic biological progression of atherosclerosis at the molecular level continues to be studied and is gradually being established (13). The existing observational studies can only provide inferences and associations between the predictive value for the development of coronary artery disease, LEAD, and physical inactivity (12).

For the past 50 years, more than 50 published studies have reported the protective effect of regular exercise on the development and deceleration of progression of CVD. Physically active cardiovascular patients

can derive significant benefits in improving the clinical manifestations of coronary heart disease and of LEAD (12,14,15). Regular physical exercise is important in secondary and tertiary prevention of coronary heart disease end points, like a second MI or premature and sudden cardiac death (16,17). Prospective (18) and retrospective (19) studies have examined the significance of physical activity on the job and during leisure time of many groups of men and a smaller number of women. Physical activity was classified based on work category, lifestyle questionnaires, interviews, and other epidemiological methods.

The presence of coronary heart disease was established by examining death certificates, hospital records, emergency room data, physicians' records, and medical evaluations or interviews with spouses or close associates. Activity levels ranged from high metabolic expenditures to minimal physical energy expenditure. There has been no uniform methodological approach to study physical inactivity as a risk factor for CVD. Most studies of sedentary lifestyle and CVD were conducted during the latter half of the previous century. There has been great variability of methodologies and data collection techniques. Nonetheless, these studies lead to certain specific suggestions. The scope of this chapter is not to present and analyze each study on physical inactivity and cardiovascular health. A comprehensive review of the scientific reports on the primary preventing effect of physical activity leads to the following conclusions:

1. Physically active people develop less coronary heart disease than their inactive counterparts (20–22), with all other variables remaining equal.
2. Whenever physically active people do develop coronary heart disease, they do so at a later age with less severe clinical manifestations (8,16,17).
3. Most studies show a consistent finding: being physically active does not increase an individual's overall risk for CVD.

The statistical significance of many published reports varies with some studies demonstrating a highly significant beneficial effect of exercise (16), and other studies showing a favorable trend, but a statistically insignificant value. A few studies showed no difference in coronary heart disease prevalence among physically active compared to physically inactive individuals.

It is a fallacy to believe that individuals with risk factors for cardiovascular events like smoking, hypertension, or hyperlipidemia can neutralize or minimize their adverse effects by exercise. In the Seven Countries Study (23,24), Finland had the highest overall prevalence of coronary heart disease. The Finnish population consumes large amounts of animal fat. Finnish lumberjacks are an example of physically active people in whom the risk for coronary heart disease remains high (25). The approach to prevent coronary heart disease should be multifaceted

and continuous. Simply put, one should modify and optimize all the modifiable known risk factors for CVD and exercise regularly.

There are several studies in the literature that show a reduction of the risk for cardiovascular events in the more physically active individuals compared to the least physically active people; between those who exercise moderately and regularly and those who do almost nothing physically (8,9,16,26). However, there is no gradient for physical exercise. There is no threshold of exercise over which there is greater benefit. In fact, there is a very small difference in risk when moderately active people are compared with very athletic individuals. On the other hand, published data show significant benefit in preventing coronary heart disease events with regular physical activities at relatively low intensity (6,8,9,16,26). Examples of moderate activity exercise include brisk walking on a horizontal level, walking upstairs, lifting and carrying light objects, light and heavy gardening, and participating in active games and sports (27). The greatest cardiovascular and overall physical, biological, and psychological benefit is derived from large muscle aerobic activity, which can substantially increase cardiac output with small increases in systolic blood pressure (28). This large muscle aerobic activity, commercially named *cardiovascular* is in contrast to heavy lifting or isometric exercise. Heavy lifting significantly increases systolic blood pressure with a relatively small increase in cardiac output. The benefit from heavy isometric exercise is small and prospectively may have a negative effect as a result of repeated elevations of the systemic arterial pressure.

A frequently asked question is about physical activity on the job. "At work I walk all over the place and carry heavy objects at times." It is true that the initial observations, which established an association between physical activity and CVD, were based on job description, e.g., the London, England bus drivers as compared to the conductors who walk on both decks of the two-decker buses issuing tickets (29,30). Similar studies have been done with truck drivers and cab drivers. It is methodologically appropriate and objective to classify people as physically inactive or active, according to the job or job description instead of questionnaires or interviews describing past physical activities. The prevalence of coronary artery disease is lower among physically active individuals by the mere job or profession, which calls for walking on a flat level for hours or climbing stairs or walking up and down hills, as many farmers and rural mailmen do. Studies performed by analyzing on-the-job activities show a protective gradient only for high level of workload. Physically active people by job necessity appear to have a decreased coronary mortality, provided that all the other risk factors remain similar or the same (31); lifting and carrying objects, walking for

a long distance, working farms, heavy labor workers, cyclist couriers, and others. These observations of on-the-job activity found the same benefit for high-intensity physical activity performed in short bursts and lower energy expenditure job activities performed during the work day for longer periods of time, e.g., railroad workers, postal workers, and others with a physically comparable workload. However, there may be a selection bias in favor of the healthier individuals who can perform physically demanding activities on the job compared to someone who is less healthy and prefers or is assigned to a desk job.

DOES ON-THE-JOB PHYSICAL ACTIVITY PROVIDE PROTECTION?

Low intensity activity on a regular basis has been reported to be inversely associated with ischemic electrocardiographic (ECG) changes. Specifically, the prevalence of ischemic changes on the resting ECG is inversely related to regular on-the-job physical activity. Job-related physical activity included walking to work among 8948 civil service workers in London, England (32). Civil servants who walked for 20 minutes or more to work on a regular basis had one-third fewer abnormalities on their resting ECG, compared to their colleagues who drove to work or took the train or bus. This inverse relationship between ECG abnormalities and regular on job physical activity could not be accounted for by differences in age, civil service grade, smoking, serum cholesterol, or glucose tolerance. The employees who walked regularly to work were also less overweight.

In England, the relation of leisure-time activity to cardiovascular mortality has been studied among middle-age employees of the civil service using a 2-day activity record procedure (33). A self-kept 48-hour record of physical activities was completed every Monday for the preceding weekend. There was a significant inverse relationship between activities requiring a peak energy expenditure of 7.5 k/cal per minute for 30 minutes or longer each day, and mortality from coronary heart disease. This protective effect of vigorous activity was not related to plasma cholesterol, blood pressure, cigaret smoking, or obesity. The benefit of vigorous activity was apparent in all age groups of participants, ranging from 40 to 69 years (33). Another study evaluated the relationship between past physical activity habits and cardiovascular health among Harvard University alumni (34). Five hundred seventy-two first MI cases were analyzed among 16,936 men between 1962 and 1972. The charts of 1413 deceased alumni between 1962 and 1978 were also examined. These analyses showed that regular post-graduation exercise of those

who did not participate in sports as college students predicted low risk for coronary heart disease. Sedentary alumni who were former athletes were at higher risk for cardiovascular events. Sedentary students who became physically active later in life gained cardiovascular protection and acquired a low risk for coronary heart disease and its complications. The results of this study are similar to several reports of job-related activity and risk for coronary heart disease; more physically active jobs early in someone's career followed by years of sedentary work resulted in higher coronary risk than the physically active individuals who continued to be physically active throughout their careers (34).

Cardiovascular mortality and physical activity was studied in a cohort of 636 healthy Finnish men age 45 to 64 years followed for 20 years (35). Approximately 39% of this cohort was classified as physically active at the onset of the study in 1964. By 1984, there were 287 deaths, 106 as a result of coronary heart disease. In the time period covering the first two-thirds of the follow-up, men with high physical activity record had lower risk of death than did men with practically no physical activity. During the last third of the study, the two survival curves gradually converged. Of the men who died, those engaged in high physical activity lived 2.1 years longer ($p = 0.002$) than those with no physical activity after adjusting for age, smoking, blood pressure, serum cholesterol, and body mass index (BMI). This significant difference was primarily a result of fewer cardiovascular deaths among the highly active group.

PHYSICAL INACTIVITY IS AN INDEPENDENT RISK FACTOR FOR THE DEVELOPMENT OF CARDIOVASCULAR DISEASE, CORONARY DISEASE, AND LOWER EXTREMITY ARTERIAL DISEASE

Regular physical activity is an independent factor in delaying sudden (premature) cardiac death among middle-age men. The relation of self-selected leisure-time physical activity to first major coronary event and overall mortality was studied in 12,138 middle age men who participated in the Multiple Risk Factor Intervention Trial (MRFIT) (36). The basic methodology of the MRFIT study was a questionnaire requesting the leisure-time physical activity for the preceding year quantified in minutes per day. The study participants were categorized as low, moderate, or high, according to the leisure-time physical activity performed. The combined rate of fatal coronary heart disease, sudden cardiac death, and all-cause mortality in the moderate category was 64%, whereas the same rate in the low leisure-time physical activity group was 73% ($p < 0.01$). Interestingly, the mortality rates of subjects with high leisure-time physi-

cal activity were similar to that of subjects with moderate leisure-time physical activity. The combined fatal and nonfatal major cardiac events were 20% lower in the high leisure-time physical activity compared to those subjects in the low leisure-time category ($p < 0.05$). Statistical adjustments for other baseline risk factors were made (36). Leisure-time physical activity has a modest inverse relationship to coronary heart disease and overall mortality in middle-age men (36). In a study in Finland (37), physical activity at work and during leisure-time was studied utilizing a questionnaire methodology. The study population consisted of 3978 men, age 30 to 59 years and 3688 women, age 35 to 59 years. The follow-up for each study participant was 7 years. Low physical activity at work was associated with an increased risk for MI, stroke, and overall mortality in both men and women even after controlling for age, serum cholesterol, diastolic blood pressure, smoking, and body weight. In this prospective study, the relative risk for MI was 1.5 (95% confidence interval 1.2–2) for men and 2.4 (95% confidence interval 1.5–3.7) for women. Men and women at highest risk for cardiovascular and overall mortality reported no vigorous exercise during work or any vigorous leisure-time exercise. Those at lowest risk reported vigorous exercise at work and off work (*see* Table 1).

WHAT IS THE RELATION OF PHYSICAL FITNESS TO FUTURE CARDIOVASCULAR EVENTS OR TOTAL MORTALITY?

This question was addressed by the Lipid Research Clinics' prevalence survey in the study of 4276 individuals age 30 to 69 years who were followed for an average of 8.5 years (39,40). Baseline assessment of individuals in this study included an analysis of the conventional coronary risk factors and treadmill exercise testing. The performance during maximal exercise was used as a measure of physical fitness. Men who had clinical evidence of CVD at baseline ($n = 649$) had their records analyzed separately. Among the remaining 3106 men, 45 deaths occurred from cardiovascular causes. After adjustment for age and known cardiovascular risk factors, a lower level of physical fitness was found to be associated with overall CVD, a higher coronary mortality, and death rate from all causes. The relative risk for cardiovascular mortality for the least-fit apparently healthy men was compared with the most fit healthy men according to their exercise capacity. The relative risk for overall cardiovascular mortality was 3.6 (95% confidence interval 1.6–5.6) ($p = 0.0004$). For death resulting from coronary heart disease the relative risk was 2.8 (95% confidence interval 1.3–6.1) ($p = 0.007$).

Table 1
Risk Ratios of Major End Points (and 95% Confidence Intervals)
by Tertile of Total Leisure-Time Physical Activities in Men in MRFIT*

<i>Tertile of leisure-time physical activities</i>			
<i>End points[†]</i>	<i>1</i>	<i>2</i>	<i>3</i>
<i>Age-Adjusted Risk Ratios</i>			
CHD death	1.00	0.63 [‡] (0.43–0.86)	0.64 [‡] (0.47–0.88)
Sudden death	1.00	0.63 [‡] (0.42–0.93)	0.65 [§] (0.44–0.96)
Fatal/nonfatal MI	1.00	0.88 (0.75–1.04)	0.81 [‡] (0.68–0.95)
All-cause deaths	1.00	0.71 [‡] (0.57–0.88)	0.83 (0.67–1.01)
<i>Risk Ratios Adjusted by Proportional Hazards Regression[¶]</i>			
CHD death	1.00	0.64 [‡] (0.47–0.88)	0.67 [§] (0.49–0.92)
Sudden death	1.00	0.64 [‡] (0.43–0.96)	0.67 [§] (0.45–1.00)
Fatal/nonfatal MI	1.00	0.90 (0.76–1.06)	0.83 [§] (0.70–0.99)
All-cause deaths	1.00	0.73 [‡] (0.59–0.91)	0.87 (0.70–1.07)

*MRFIT indicates Multiple Risk Factor Intervention Trial.

[†]CHD, coronary heart disease; MI, myocardial infarction.

[‡] $p < .01$.

[§] $p < .05$.

^{||} $p < .07$.

[¶]Regression of end points of age (years), levels of diastolic blood pressure (mmHg), total cholesterol (mmol/L [mg/dL]), number of cigarettes per day, and treatment group (1. special intervention; and 2. usual care).

From Leon et al. (38).

Highly significant associations were also seen for vasculopathic men. A low level of physical fitness in vasculopathic men was associated with a higher risk of death, particularly from cardiovascular events (39,40). This higher risk for death in the sedentary patients is a risk factor, separate and independent of the known risk factors for coronary artery disease and LEAD. It should be emphasized that physical fitness in this study was at least a regular walk on the treadmill; there was a close relationship of physical characteristics and life habits to treadmill exercise capacity (41).

In a separate study, the Cooper Clinic (Dallas, TX) (42) investigators studied the relationship of physical fitness, as measured by maximal treadmill performance, to all-cause and cause-specific mortality in 10,224 men and 3120 women who completed comprehensive medical examinations. The average follow-up was slightly more than 8 years. There were a total of 110,482 person-years of observation. During this

time, 240 men and 43 women died. Age-adjusted all-cause mortality rates declined across physical fitness quintiles from 64.0 per 10,000 person-years in the least-fit men to 18.6 per 10,000 person-years in the most-fit men. Corresponding values for women were 39.5 per 10,000 person-years to 8.5 per 10,000 person-years. These statistical inferences were validated after adjustment for age, smoking, cholesterol levels, systolic blood pressure, fasting blood glucose level, and family history for coronary artery disease (42).

HIGHER LEVELS OF PHYSICAL FITNESS DELAY ALL-CAUSE MORTALITY AND CARDIOVASCULAR MORTALITY IN PARTICULAR

The relation of maximal oxygen uptake (measured during maximal exercise on a stationary bicycle) to cardiovascular mortality was studied in 2014 Norwegian men 40 to 59 years of age at the beginning of the study, with a follow-up period of 16 years (9). The relative risk of death from any cause in men in the fourth (highest) fitness quartile was compared with that in men in the first (lowest) quartile. The relative risk for total mortality in the highest fitness quartile was 0.54 after adjustment for age, smoking, serum lipid levels, blood pressure, resting heart rate, vital capacity, BMI, and glucose tolerance. Total mortality was similar among subjects in the three lowest quartiles. The adjusted relative risk of death from cardiovascular events in the highest quartile compared to the lowest was 0.41 ($p = 0.013$). The relative risks for the third and second quartiles (compared with the lowest) were 0.45 ($p = 0.026$) and 0.59 ($p = 0.15$), respectively (9).

The least fit and the least active have the highest rate for cardiovascular morbidity and mortality. Moderate increases in physical fitness and activity such as a daily brisk walk for half an hour, are associated with a significant reduction in risk. There is a small dose–response relation at higher levels of activity and fitness. However, the magnitude of the benefit declines rapidly as fitness levels increase (43).

DOES MODERATE DAILY EXERCISE HAVE AN IMPACT ON SECONDARY PREVENTION OF CORONARY HEART DISEASE?

In addition to studies that have compared morbidity and mortality rates in physically active and inactive cardiac patients, controlled studies show that patients with a history of MI randomly assigned to exercise and control groups demonstrate a trend of lower mortality in the more

physically active post-MI patients (44). Benefit apparently derived from an increase in caloric expenditure of no more than 300–400 kcal per session three to four times per week at a moderate intensity (60 to 75% of maximal exertion or functional aerobic capacity) (44).

Randomized clinical trials of physical rehabilitation after MI tend to demonstrate lower mortality in treated (rehabilitated) patients. Meta-analyses of studies performed in the early 1980s showed a lower mortality in those patients who participated in cardiac rehabilitation as compared to those who did not (45,46).

PROPOSED BIOLOGICAL MECHANISMS BY WHICH EXERCISE MAY CONTRIBUTE TO THE PRIMARY OR SECONDARY PREVENTION OF CORONARY HEART DISEASE

Exercise can:

- Maintain or increase myocardial oxygen supply (47,48)
- Delay progression of coronary atherosclerosis (49–51)
 - Improve lipoprotein profile (increase HDL/LDL-cholesterol ratio) (52)
 - Improve carbohydrate metabolism (increase insulin sensitivity) (probable)
 - Decrease platelet aggregation and increase fibrinolysis (53)
 - Decrease adiposity (51,54,55)
- Increase coronary collateral vessel formation
- Increase epicardial artery diameter (51,54,55)
- Increase coronary blood flow (myocardial perfusion) or distribution
- Decrease myocardial work and oxygen demand (56–58)
- Decrease heart rate at rest and submaximal exercise (59)
- Decrease systolic and mean systemic arterial pressure following regular submaximal exercise (60,61)
- Increase cardiac output during submaximal exercise (62,63)
- Decrease circulating plasma catecholamine levels (decrease sympathetic tone) at rest and during submaximal exercise (64)
- Increase stroke volume at rest and during submaximal and maximal exercise (65,66)
- Increase ejection fraction at rest and during exercise (67)
- Increase intrinsic myocardial contractility (68)
- Increase left ventricular myocardial function by decreasing afterload
- Increase electrical stability of the myocardium (38,51,55,69)
- Decrease regional ischemia following a regular program of submaximal exercise (51,55,69)
- Increase ventricular fibrillation threshold (38,51,55,69)

Exercise also:

- Improves carbohydrate metabolism (70)
- Improves fat metabolism (71)
- Improves muscle endurance (72)
- Enhances endorphin release (70)
- Improves self-esteem (72)

We should make every effort in prescribing the appropriate diet and motivate every patient to become physically active. In a broad sense, regular physical activity is of paramount importance for every patient. It has short-term benefits and long-term dividends, both biologically and psychologically. The mission of every health care provider is to prolong life and improve the quality of life.

REFERENCES

1. Diabetes Prevention Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; 346:393–403.
2. Kokkinos P, Narayan P, Papademetriou V. Exercise as Hypertension Therapy. *Card Clinics* 2001; 19:507–516.
3. Kokkinos P, Fernhall B. Physical activity and high density lipoprotein cholesterol levels: What is the relationship? *Sports Medicine* 1999; 28:307–314.
4. Bijnen FC, Caspersen CJ, Mosterd WL. Physical inactivity as a risk factor for coronary heart disease: a WHO and International Society and Federation of Cardiology position statement. *Bulletin of the World Health Org* 1994; 72:1–4.
5. U.S. Public Health Service. Healthy people 2000: national health promotion and disease prevention objectives—full report and commentary. DHHS publication no. (PHS) 91–50212. Washington, DC: U.S. Department of Health and Human Services, 1991.
6. American College of Sports Medicine. The recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness in healthy adults. *Med Sci Sports Exerc* 1998; 30:975–991.
7. Eaton CB. Relation of physical activity and cardiovascular fitness to coronary heart disease, Part II: Cardiovascular fitness and the safety and efficacy of physical activity prescription. *J Am Board Fam Practice* 1992; 5:157–165.
8. Kannel WB, Belanger A, D’Agostino R, Israel I. Physical activity and physical demand on the job and risk of cardiovascular disease and death: the Framingham Study. *Am Heart J* 1986; 112:820–825.
9. Sandvik L, Erikssen J, Thaulow E, Erikssen G, Mundal R, Rodahl K. Physical Fitness as a Predictor of Mortality among Healthy, Middle-Aged Norwegian Men. *N Eng J Med* 1993; 328:533–537.
10. Ekroth R, Dahllöf AG, Gundeval B, Holm J, Schersten T. Physical training of patients with intermittent claudication: Indications, methods, and results. *Surgery* 1978; 84:640–643.
11. Alpert JS, Larsen A, Lassen NA. Exercise and intermittent claudication: Blood flow in the calf muscle during walking studied by the Xenon-133 method. *Circulation* 1969; 89:353–359.

12. Gardner AW, Poehlman ET. Exercise rehabilitation programs for the treatment of claudication pain: A meta-analysis. *JAMA* 1995; 274:975–980.
13. Soofi M, Satter AM, Maisch B, Schaefer JR. Molecular mechanisms involved in atherosclerosis. *Herz* 2002; 27:637–648.
14. Hiatt WR, Regensteiner JG, HArgarten ME, Wolfel EE, Brass EP. Benefit of exercise conditioning for patients with peripheral arterial disease. *Circulation* 1990; 81:602–609.
15. Franklin BA, Gordon S, Timmis GC. Amount of exercise necessary for the patient with coronary artery disease. *Am J Cardiol* 1992; 69:1426–1431.
16. Oberman A. Exercise and the primary prevention of cardiovascular disease. *Am J Card* 1985; 55:10D–20D
17. Leon AS. Physical activity levels and coronary heart disease. Analysis of epidemiologic and supporting studies. *Med Clinics of N Am* 1985; 69:3–20.
18. Blair SN, Kohl HW III, Barlow CE, Paffenbarger RS, Jr, Gibbons LW, Macera CA. Change in physical fitness and all-cause mortality: a prospective study. *JAMA* 1995; 273:1093–1098.
19. Morris JN, Clayton DJ, Everitt MG, Semmence AM, Burgess EH. Exercise in leisure-time: coronary attack and death rates. *Br Heart J* 1990; 63:325–334.
20. Powell KE, Thompson PA, Caspersen CJ, Kendrick JS. Physical activity and coronary heart disease. *Annu Rev Public Health* 1987; 8:253–287.
21. Berlin JA, Colditz A. A meta-analysis of physical activity in the prevention of coronary heart disease. *Am J Epidemiol* 1990; 132:612–627.
22. Paffenbarger RS Jr, Hyde RT, Wing AL, Lee IM, Jung DL, Kampert JB. The association of changes in PA level and other lifestyle characteristics with mortality among men. *N Engl J Med* 1993; 328:538–545.
23. Blackburn H, Taylor HL, Keyes A. Coronary heart disease in seven countries. *Circulation* 1970; 41:154–195.
24. Keys A. Seven countries: a multivariate analysis of death and coronary heart disease. A Commonwealth Fund Book. Cambridge Mass.: Harvard University Press, 1980.
25. Punsar S, Karvonen MJ. Physical activity and coronary heart disease in populations from east to west Finland. *Adv Cardiol* 1976; 18:196–207.
26. Kessaniemi YA, Danforth EJ, Jensen MD, et al. Dose-response issues concerning physical activity and health: an evidence-based symposium. *Med Sci Sports Exercise* 2001; 33:S351–S358.
27. Blair SN, Kohl HW, Gordon NF, Paffenbarger RS Jr. How much physical activity is good for health? *Ann Review of Pub Health* 1992; 13:99–126.
28. American College of Sports Medicine. Guidelines for exercise testing and prescription. 4th ed. Philadelphia: Lea & Fibiger, 1991, pp.93–119.
29. Morris JN, Heady J, Raffle P. Physique of London busmen. *Lancet* 1956; ii: 569–570.
30. Morris JN. Physical inactivity and coronary heart disease. *Acta Cardiol* 1974; suppl 20: 95–103.
31. Fox SM, Skinner JS. Physical activity and cardiovascular health. *Am J Cardiol* 1964; 14:731–746.
32. Rose G. Physical activity and coronary heart disease. *Proc. R. Soc. Med.* 1969; 62: 1183–1188.
33. Chave SP, Morris JN, Moss S, Semmence AM. Vigorous exercise in leisure time and the death rate: a study of male civil servants. *J Epidemiology Comm Health* 1978;32:239–243.
34. Paffenbarger RS Jr, Hyde RT, Wing AL, Hsieh CC. Physical activity, all-cause mortality, and longevity of college alumni. *N Eng J Med* 1986; 314:605–613.

35. Marti B, Pekkanen J, Nissinen A, Ketola A, Kivela SL, Punsar S, Karvonen MJ. Association of physical activity with coronary risk factors and physical ability: twenty-year follow-up of a cohort of Finnish men. *Age and Ageing* 1989; 18: 103–109.
36. The multiple risk factor intervention trial (MRFIT). A national study of primary prevention of coronary heart disease. *JAMA* 1976; 235:825–827.
37. Salonen JT, Puska P, Tuomilehto J. Physical activity and risk of myocardial infarction, cerebral stroke and death. *Am J Epidemiol* 1982; 115:526–537.
38. Leon AS, Connett J, Jacobs DR, Rauramaa R. Leisure-time physical activity levels and risk of coronary heart disease and death. *JAMA* 1987;258:2388–2395.
39. Rifkind BM. Plasma Lipid Distributions in selected North American populations: The Lipid Research Clinics Program Prevalence Study. *Circulation* 1979; 60:427–439.
40. Williams DO, Mowery RL, Waldman GT. Common methods, different populations. The Lipid Research Clinics Program Prevalence Study. *Circulation* 1980;62:18.
41. Leon AS, Jacobs DR Jr, DeBacker G, Taylor HL. Relationship of physical characteristics and life habits to treadmill exercise capacity. *Am J Epidemiol* 1981; 113:653–660.
42. Blair SN, Kohl HW, Barlow CE. Physical Activity, Physical Fitness, and All-Cause Mortality in Women: Do Women Need to be Active? *J Am Coll Nutr* 1993; 12: 368–371.
43. Bruce RA, DeRouen TA, Hossack KF, Blake B, Hofer V. Value of maximal exercise tests in risk assessment of primary coronary heart disease events in healthy men. *Am J Cardiol* 1980; 46:371–378.
44. Blumenthal JA, Rejeski WJ, Walsh-Riddle M, Emery CF, Miller H, Roark S, Ribisl PM, Morris PB, Brubaker P, Williams RS. Comparison of high- and low-intensity exercise training early after acute myocardial infarction. *Am J Cardiol* 1988; 61: 26–30.
45. O'Connor GT, Buring JE, Yusuf S, Goldhaber SZ, Olmstead EM, Paffenbarger RS Jr, Hennekens CH. An overview of randomized trials of rehabilitation with exercise after myocardial infarction. *Circulation* 1989; 80:234–244.
46. Oldridge NB, Guyatt GH, Fischer ME, Rimm AA. Cardiac rehabilitation after myocardial infarction: combined experience of randomized clinical trials. *JAMA* 1991; 266:1535–1542.
47. Hansen JE, Sue DY, Wasserman K. Predicted values for clinical exercise testing. *Am Rev Respir Dis* 1984; 129(suppl):549.
48. Bassett D, Howley E. Maximal oxygen uptake: “classical” versus “contemporary” viewpoints. *Med Sci Sports Exerc* 1997; 29:591.
49. Leon AS. Contribution of regular moderate-intensity physical activity. In: Leon AS, ed. *Physical Activity and Cardiovascular Health: A National Consensus*. Champaign, Ill: Human Kinetics; 1997:55–66.
50. Leon AS. Effects of exercise conditioning on physiologic precursors of coronary heart disease. *J Cardiopulm Rehabil* 1991; 11:46–57.
51. Leon AS, Richardson M. Exercise, health, and disease. In: Roberts SO, Robergs RA, Hanson P, eds. *Clinical Exercise Testing and Prescription: Theory and Application*. Boca Raton, Fla. CRC Press; 1997:281–302.
52. Tran ZV, Weltman A. Differential effects of exercise on serum lipid and lipoprotein levels seen with changes in body weight: a meta-analysis. *JAMA* 1985; 254:919–924.
53. Stratton JR, Chandler WL, Schwartz RS, et al. Effects of physical conditioning on fibrinolytic variables and fibrinogen in young and old healthy adults. *Circulation* 1991; 83:1692–1697.

54. Kramsch DM, Aspen AJ, Abramowitz BM, et al. Reduction of coronary atherosclerosis by moderate conditioning exercise in monkeys on an atherogenic diet. *N Engl J Med* 1981; 305:1483-1489.
55. Squires RW. Mechanisms by which exercise training may improve the clinical status of cardiac patients. In: Pollock ML, Schmidt DH, eds. *Heart Disease and Rehabilitation*, 3rd ed. Champaign, Ill: Human Kinetics; 1995:147-160.
56. Ehsani A, Martin W, Heath G, et al. Cardiac effects of prolonged and intense exercise training in patients with coronary artery disease. *Am J Cardiol*. 1982; 50: 246-254.
57. Niebauer J, Hambrecht R, Velich T, et al. Attenuated progression of coronary artery disease after 6 years of multifactorial risk intervention: role of physical exercise. *Circulation* 1997; 96:2534-2541.
58. Gould KL, Ornish D, Kirkeeide R, et al. Improved stenosis geometry by quantitative coronary arteriography after vigorous risk factor modification. *Am J Cardiol*. 1992; 69:845-853.
59. Goldsmith RL, Bigger JT Jr, Steinman RC, et al. Comparison of 24-hour parasympathetic activity in endurance-trained and untrained young men. *J Am Coll Cardiol* 1992; 20: 552-558.
60. Paffenbarger RS Jr, Wing AL, Hyde RT, et al. Physical activity and incidence of hypertension in college alumni. *Am J Epidemiol* 1983; 117: 245-257.
61. Blair SN, Goodyear NN, Gibbons LW, et al. Physical fitness and incidence of hypertension in healthy normotensive men and women. *JAMA* 1984; 252:487-490.
62. Hartley LH, Grimby G, Kilbom A, et al. Physical training in sedentary middle-aged and older men: cardiac output and gas exchange during submaximal and maximal exercise. *Scand J Clin Lab Invest* 1969; 24:335-344.
63. Gerstenblith G, Lakatta EG, Weisfeldt ML. Age changes in myocardial function and exercise response. *Prog Cardiovasc Dis* 1976; 19:1.
64. Hartley LH, Mason JW, Hogan RP, et al. Multiple hormonal responses to prolonged exercise in relation to physical training. *J Appl Physiol* 1972; 33:607-610.
65. Weber KT, Janicki JS. Cardiopulmonary exercise testing for evaluation of chronic cardiac failure. *Am J Cardiol* 1985; 55:22A.
66. Blomquist CG, Saltin B. Cardiovascular adaptations to physical training. *Annu Rev Physiol* 1983; 45:169.
67. Oberman A, Fletcher GF, Lee J, et al. Efficacy of high-intensity exercise training on left ventricular function in normal subjects: a longitudinal study by radionuclide angiography. *Am J Cardiol* 1980; 45:244-252.
68. Scheuer J. Physical training and intrinsic cardiac adaptations. *Circulation* 1973; 47:677-680.
69. Haskell WL. Sedentary lifestyle as a risk factor for coronary heart disease. In: Pearson TA, ed. *Primer in Preventive Cardiology*. Dallas, TX: American Heart Association, 1994: 173-187.
70. Orten JM, Neuhaus OW. *Human Biochemistry*. St. Louis: CV Mosby. 1982.
71. Phillips SM, Green HJ, Tarnopolsky MA, et al. Effects of training duration on substrate turnover and oxidation during exercise. *J Appl Physiol* 1996; 81:2182.
72. Pollack ML, Miller HS, Linnerud AC, Cooper KH. Frequency of training as a determinant for improvement in cardiovascular function and body composition of middle-aged men. *Phys Med Rehab* 1975; 58:141-145.

8

Pathogenesis of Atherosclerotic Vascular Disease

*Bassem Jamil Basha, MD,
George L. Bakris, MD, FACP, FAHA, FASN
and James R. Sowers, MD*

CONTENTS

INTRODUCTION
RHEOLOGY
BLOOD CELLS, VASCULAR INJURY, AND THROMBOSIS
THE ENDOTHELIUM
THE ROLE OF INSULIN RESISTANCE AND HYPERURICEMIA
THE ROLE OF DIETARY CONSTITUENTS
OBESITY
ALCOHOL
SMOKING
HOMOCYSTEINE
INFLAMMATION
INFECTIONS
PATHOLOGY OF ATHEROMA
GROWTH FACTORS, CYTOKINES, AND MITOGENESIS
LIPOPROTEINS
EXTRACELLULAR MATRIX
PHYSIOLOGICAL ANTAGONISTS OF ATHEROSCLEROSIS
REFERENCES

From: *Clinical Hypertension and Vascular Diseases: Lower Extremity Arterial Disease*
Edited by: D. G. Caralis and G. L. Bakris © Humana Press Inc., Totowa, NJ

INTRODUCTION

Epidemiological studies have identified risk factors for coronary heart disease (CHD) and its underlying pathology: atherosclerosis. Genetic and environmental factors interact to shape an individual's age-related risk of atherosclerosis (1,2). In the Framingham Heart Study, substantial proportion of the variability in carotid intima-media thickness (IMT) is explained by genetic factors (3). The role of gene polymorphism has been reviewed in ref. 4.

Natural History

Intrauterine undernutrition leads to changes of fetal growth and metabolism, and programs later development of CHD risk factors: hypertension, impaired glucose, and cholesterol metabolism are affected by intrauterine growth (5); even hypercholesterolemia during pregnancy determines long-term susceptibility of children to atherosclerosis (6). Body fat is a good indicator for future coronary artery disease (CAD) in 9- to 10-year-old boys and girls (7).

In 3000 autopsies of persons aged 15–34 whose deaths were caused by either accident, homicide, or suicide, the extent of fatty streaks and raised lesions in the right coronary artery (RCA) and abdominal aorta positively correlated with high-density lipoprotein cholesterol (HDL-C), hypertension, impaired glucose tolerance (IGT), and obesity. Because they also were associated negatively with HDL-C and positively with smoking for atherosclerosis of the abdominal aorta, controlling risk factors should start in adolescence (8).

It was suggested that for lesions starting in young people the role of endothelial dysfunction, decreased nitric oxide (NO), and increased adhesive molecules predominate, whereas for lesions starting in older people the role of metabolic changes of the endothelium and alteration in the extracellular matrix (ECM) predominate (9).

Risk Factors

In a community-based study in Taiwan, hypertension was found to strongly influence carotid atherosclerosis (10). In addition, the fasting insulin and insulin/glucose ratio are independent risk factors for the accelerated development of CAD (11,12). However, it should be noted that the administration of exogenous insulin or the sulphonylureas, which are insulin secretagogues, did not increase cardiovascular disease (CVD) especially exogenous insulin. Thus, insulin may not be the primary culprit implicated in the increased mortality from CHD (13).

Microalbuminuria in healthy subjects is associated with atherosclerotic risk factors such as increased systolic and diastolic blood pressure (BP) decreased Apo A1 and HDL-C levels (12). Minor derangements of renal function are associated with an increase in CVD risk factors and promote progression of atherosclerosis (reviewed in ref. 14). However, in a separate study in contrast to BP, body mass index (BMI), and triglycerides (TGs), there was no relation between urinary albumin excretion and flow-mediated vasodilation in apparently healthy subjects. This suggests that the presence of atherogenic risk factors precedes the development of endothelial dysfunction in microalbuminuric but otherwise healthy subjects (15).

A summary of risk factors associated with the development of CHD from atherosclerosis is summarized in Table 1. Those with the strongest relationship with CHD are low-density lipoprotein-cholesterol (LDL-C), total cholesterol (TC), and the total cholesterol/high-density lipoprotein cholesterol (TC/HDL-C) ratio (1).

RHEOLOGY

Patients with hypertension have increased common carotid artery IMT and lower mean shear stress with a negative correlation between shear stress and IMT in hypertensives. In the general population, decreased shear stress may contribute to atherosclerosis (16). It was suggested that the ubiquitous atherosclerotic changes in fetal and pediatric subjects when serum cholesterol levels are normal demonstrate the importance of repetitive hemodynamic stresses, rather than hypercholesterolemia, in atherosclerosis (reviewed in ref. 17).

Local blood flow conditions modulate the production of vasoactive substances, NO and endothelin (ET)-1, by human umbilical vein endothelial cells (HUVEC) (18) and shear stress upregulates monocyte chemoattractant factor (MCP)-1, interleukin (IL)-8, ET-1, and connective tissue growth factor (CTGF) (19) and induces collagen XII expression, which may stabilize the vascular structure in HUVEC (20).

Laminar flow exposure leads to activation of antioxidant genes in endothelial cell (EC) (21) and promotes EC survival and quiescence and the secretion of substances that promote vasodilation and anticoagulation (22). Flow induces an increase in oxidative stress in EC, which is dependent on the pulsatile nature of flow (23).

In rabbits, exposure of the arterial wall to low wall shear stress may activate ECs increasing intercellular permeability, which in turn increases the vulnerability of these regions to atherosclerosis (24).

Table 1
Some Factors Associated With Development of Atherosclerosis

LDL-cholesterol*
Total cholesterol*
Total cholesterol/HDL*
Smoking*
Increased triglycerides
Hypertension
Obesity
Diabetes
Left ventricular hypertrophy
Hyperinsulinemia
Increased fibrinogen
Herpes infection
Lp(a)
Homocysteine
Chlamydia pneumoniae
Hypothyroidism
CRP
PAF-AH
LPL
Phospholipase aII
Low wall shear stress

*Indicates the strongest correlation with atherosclerosis development.

Also, the role of L-selectin in various situations of leukocytes recruitment could be affected, among other reasons, by wall shear (25). L-selectin is a leukocyte adhesion molecule that is rapidly shed after leukocyte activation so that it appears to be decreased in CAD (26).

Pulsatile oscillatory shear stress induces a procoagulant phenotype of human EC by increasing tissue factor mRNA and protein expression and activity (27).

BLOOD CELLS, VASCULAR INJURY, AND THROMBOSIS

Vascular injury and thrombosis are common initial events in atherosclerosis (reviewed in ref. 28). Intrinsic pathway enhances the thrombogenicity of atherosclerotic lesions after the removal of the endothelial layer and exposure of smooth muscle cells (SMCs) and macrophages to blood flow (29). Studies on plasma levels of tissue factor pathway inhibitor (TFPI) in patients with various diseases suggest that TFPI (a Kunitz-type protease inhibitor that inhibits the initial reactions of blood

coagulation) may be a marker of EC dysfunction (30). Patients suffering from proven peripheral artery disease (PAD) have higher plasma levels of tissue factor (TF) and vascular endothelial growth factor (VEGF) compared with controls, with a significant correlation between the two. This suggests a link between the hypercoagulable state in PAD and the process of angiogenesis (31).

Plasminogen activator inhibitor (PAI)-1 plasma levels depend on gene regulation, insulin resistance, diabetes mellitus (DM), hypertriglyceridemia, and activated renin angiotensin system through a receptor-dependent mechanism (reviewed in ref. 32). In Apo E $-/-$ PAI-1 $-/-$ mice, loss of PAI-1 promoted the growth of advanced atherosclerotic plaques as a result of enhanced ECM deposition. Also, plaques exhibited collagen fiber disorganization and degradation; therefore, though PAI-1 may promote plaque growth caused by its antifibrinolytic properties, PAI-1 has a protective role by limiting plaque growth and preventing abnormal matrix remodeling (33).

Annexin (AN) II is a coreceptor on ECs for plasminogen and tissue plasminogen activator (tPA). Recombinant AN II enhanced plasmin generation on HUVECs in vitro, reduced thrombus formation in a rat carotid artery thrombus model (34), and increased urokinase plasminogen activator (uPA) expression in atherosclerotic arteries contribute to intimal growth and constrictive remodeling leading to lumen loss (although increased uPA expression in EC decreases intravascular thrombosis) (35).

Tissue transglutaminase (tTG), a family of enzymes catalyzing the formation of stable covalent crosslinks between proteins, are upregulated by thrombin in HUVEC and have a role in the stabilization of atherosclerotic plaques (36).

In a cross-sectional study, the presence and extent of atherosclerosis, as measured by ultrasound, correlated positively with plasma fibrinogen (37). Plasma fibrin D-dimer levels are strongly and independently associated with the presence of CAD in patients with stable angina (38). However, there is doubt about its etiologic contribution because elevated plasma fibrinogen concentrations in Apo E*3-Leiden transgenic mice do not affect the progression of diet-induced atherosclerotic lesions (39). γ A/ γ fibrinogen is a fibrinogen isoform that constitute 15% of total plasma fibrinogen. It contains an additional binding site for factor XIII and active thrombin, and forms fibrin clots that are resistant to fibrinolysis in vitro. This isoform is not associated with age or gender, and was higher in CAD patients than controls independent of total fibrinogen levels (which rises with age and are higher in women) (40).

Mast cell (MC), the high basal cardiac and serum histamine in Apo E k/o mice, along with the high number of cardiac mast cells, suggest possible ongoing cardiac mast cell activation that may participate in atherosclerosis (41).

Activated MCs may participate in the weakening and rupture of atherosclerotic plaques by causing the loss of matrix-synthesizing SMC by inhibiting the proliferation of SMCs *in vitro* and reducing their ability to produce collagen. Chymase, a neutral serine protease secreted by activated mast cells, can also inhibit SMC-mediated collagen synthesis, and moreover cause degradation of the collagen matrix by activating latent interstitial collagenase (matrix metalloproteinase [MMP]-1). Furthermore, chymase can induce SMC apoptosis (reviewed in ref. 42).

MC chymases also degrade Apo E and apo angiotensin II (AII) and inhibit the apoprotein-mediated removal of macrophage cholesterol in Apo A1 knockout (KO) mice (43). Chymase and angiotensin converting enzyme (ACE) regulate AII production in distinct tissue compartments (44).

Platelets produce NO, which is increased by the dietary supplementation of L-arginine to hypercholesterolemic rabbits. This effect is associated with reduced platelet aggregation (45). Platelet activation is increased in patients with CAD (46). Hypercholesterolemia primes human platelets for recruitment to lesion-prone sites via endothelial von Willebrand factor (vWF), platelet GP1b α , and platelet p-selectin before lesions are detectable (47).

Platelet factor 4 (PF4), a cationic protein released by activated platelets, inhibits the catabolism of LDL. Retention of LDL complexes on cell surfaces may facilitate pro-atherogenic modification (48), such as promoting oxidized oxLDL formation, binding to oxLDL directly, increasing oxLDL binding to vascular cells and macrophages, and increasing the amount of oxLDL esterified by macrophages (49).

Activated platelets stimulate MCP-1 and intercellular adhesion molecule (ICAM)-1 of HUVECs (50). Circulating activated platelets bind to leukocytes, preferentially monocytes, to form platelet-monocyte/leukocyte aggregates that interact with atherosclerotic lesions leading to the delivery of the platelet-derived chemokines and platelet factor 4 (CXCL4) to the monocyte surface and endothelium of atherosclerotic arteries (51).

Receptors for extracellular nucleotides, the P2 receptors, have been recognized as fundamental modulators of leukocytes, platelets, SMCs and EC, P2 receptors mediate chemotaxis, cytokine secretion, NO generation, platelet aggregation, and cell proliferation in response to accumulation of nucleotides into the extracellular milieu. Clinical trials have

shown the benefit of antagonists of the adenosine diphosphate (ADP) platelet receptor(s) in the prevention of vascular accidents in patients with atherosclerosis (reviewed in ref. 52).

Activated macrophages stimulate angiogenesis that can further recruit inflammatory cells and more angiogenesis. Plaque angiogenesis promotes the growth of atheromas and the angiogenesis inhibitor, angiostatin, reduces plaque angiogenesis and inhibits atherosclerosis (53).

THE ENDOTHELIUM

Endothelial dysfunction is an independent predictor of cardiovascular events (reviewed in ref. 54); different risk factors cause endothelial dysfunction probably through increased oxidative stress and/or inflammation (reviewed in ref. 55).

The endothelium has a strong role in atherosclerosis. The specific EC markers, soluble E-selectin, vWF, and soluble thrombomodulin were examined; patients with symptomatic PAD have increased vWF (as a marker of generalized atherosclerosis) and soluble thrombomodulin (as a marker of disease extent), but not soluble E-selectin (56).

NO is a vasodilator and inhibits vascular SMC (VSMC) proliferation, leukocyte adherence to endothelium, and platelet adhesion and aggregation (57).

There are three different forms of NO synthase (NOS):

1. Endothelial NOS (eNOS) is responsible for producing NO in the vascular wall (reviewed in ref. 58). In rat aortic EC, acute exposure to both estradiol and insulin-like growth factor (IGF)-1 was associated with an increase in eNOS activity (59). The presence of abnormal ECM in the vessel wall could be responsible for decreased NO synthesis (60), however, chronic over expression of eNOS accelerates atherosclerosis under hypercholesterolemia. eNOS dysfunction, demonstrated by lower NO production relative to eNOS expression and enhanced superoxide production in the endothelium, appears to play important roles in the progression of atherosclerosis in Apo E KO/eNOS transgenic mice (61).
2. Inducible NOS (iNOS) expression and the resultant increased NO production are associated with atherosclerotic lesions (62). iNOS activity and gene transcription in VSMC was increased following exposure to IGF-I which was reduced by AII pretreatment (63).
3. Neuronal NOS (nNOS) plays important roles in suppressing arteriosclerotic vascular lesions (64).

In patients with atheromas levels of asymmetric dimethylarginine (ADMA), an endogenous inhibitor of NOS, are increased and correlated with endothelial dysfunction (reviewed in ref. 57). Dimethylarginines

are the result of the degradation of methylated proteins. ADMA is metabolized by the enzyme dimethylarginine dimethylaminohydrolase (DDAH); DDAH activity and/or expression may therefore contribute to the pathogenesis of endothelial dysfunction in various diseases (reviewed in ref. 65).

L-arginine supplementation does not affect lesion formation in western type diet-fed Apo E KO mice, but it negates the protective effect of iNOS gene deficiency in Apo E/iNOS double KO mice suggesting that L-arginine supplementation may paradoxically contribute to, rather than reduce, lesion formation by mechanisms that involve lipid oxidation, peroxynitrite formation, and NOS uncoupling (66).

Serum levels of soluble adhesion molecules in patients with stable angina are comparable to those of healthy persons. Unstable angina is characterized by significant elevation of sP-selectin and soluble vascular cell adhesion molecule (sVCAM)-1 serum levels (67).

In ECs, oxLDL suppressed basic fibroblast growth factor (bFGF) expression and DNA synthesis, so atherosclerosis was associated with impaired bFGF-dependent EC growth (68). VEGF serum levels were increased in CAD and PAD compared with controls. Flt-1 is VEGF receptor, soluble Flt-1 was lower in patients with PAD, but not CAD, compared with controls (69). VEGF promotes neovascular growth as is oxidative stress: in human and rat VSMC, reactive oxygen species (ROS) enhance neovascularization and VEGF protein and mRNA expression (70). VEGF, in cholesterol-fed mice doubly deficient in Apo E/Apo B100, increased macrophage in bone marrow and blood, and increased plaque area and plaque macrophage and EC content. The same results hold true for rabbits (71).

EC synthesize and secrete proteoglycans (72). Accumulation of proteoglycans in the intimal atherosclerotic lesions may predispose to further lipid accumulation, calcification, and thrombosis. One of the proteoglycans, heparan sulfate, interacts with antithrombin III giving ECs a nonthrombogenic surface. A threshold concentration for LDL may exist above, which there is an exponential irreversible increase in EC permeability that was associated with a decrease in basement membrane-associated heparan sulfate proteoglycan (HSPG) content. This increased permeability could be induced by antiserum against the core protein of HSPG (73).

oxLDL, oxidative stress, and AII can induce EC apoptosis that can compromise vasoregulation, increased SMC proliferation, SMC migration, and blood coagulation (reviewed in ref. 74). Progressive telomere shortening in vivo has been observed in regions susceptible to athero-

sclerosis, vascular EC with senescence-associated phenotypes are present in human atherosclerotic lesions and EC senescence induced by telomere shortening showed increased ICAM-1 expression and decreased eNOS activity, contributing to atherogenesis (75). Ageing in the liver is associated with pseudocapillarization of the sinusoidal endothelium that results in impaired clearance of chylomicron remnants, postprandial hypertriglyceridemia, and atherosclerosis (there is loss of pores which normally allows passage of chylomicron remnants for uptake and metabolism by hepatocytes) (reviewed in ref. 76).

THE ROLE OF INSULIN RESISTANCE AND HYPERURICEMIA

Insulin stimulates Ca-ATPase, Na-K-ATPase, and PI3K and decreases calcium influx into VSMC. Therefore, insulin resistance causes increased intracellular ionized calcium and reduced intracellular Mg ion concentration that has been associated with vasospasm, increased vascular reactivity, increased intracellular calcium concentration, the formation of pro-inflammatory agents, oxygen radicals, platelet aggregation, decreased cardiac bioenergetics, cardiac failure, lipoprotein oxidation, gender-related modulation of NO, increased vWF and oxygen free radical activity reflecting endothelial dysfunction and oxidative stress, and changes in membrane fatty acid saturation (11,77).

However, postprandial hyperinsulinemia is independently associated with CAD irrespective of fasting glucose, postprandial glucose, and fasting insulin levels in nondiabetic women with clustering of factors of the metabolic syndrome (78).

Insulin stimulates tumor necrosis factor (TNF)- α production in macrophages (79); TNF- α could play a role in the development of insulin resistance in humans, both in muscle and in vascular tissue (80).

The adipocyte-derived hormone, adiponectin, accumulates in the injured artery from the plasma and suppresses endothelial inflammatory response and VSMC proliferation, as well as macrophage-to-foam cell transformation in vitro. In Apo E KO mice, adiponectin treatment led to inhibition of lesion formation with smaller lipid droplets in the lesions, and suppressed mRNA of VCAM-1 and class A scavenger receptor (SR). Adiponectin migrates to foam cells in the fatty streak lesions (81).

Hyperuricemia, related to decreased renal blood flow, accompanies nephrosclerosis, predates proteinuria, and follow left ventricular hypertrophy. In the UKPDS, macrovascular and microvascular complications were reduced by BP and blood glucose control (82).

THE ROLE OF DIETARY CONSTITUENTS

Polyunsaturated Fatty Acids

In a cross-sectional study, a higher intake of linoleic or linolenic acid was inversely related to the prevalence odds ratio of CAD in humans (83). Polyunsaturated fatty acids (PUFA) have anti-atherosclerotic effects that appear to be caused by several mechanisms:

- 1) Modification of the arachidonic acid (AA) cascade (84).
- 2) Reduction of monocyte production of platelet activating factor (PAF) (85).
- 3) Inhibition of coagulation (86).
- 4) Reduction in synthesis and action of peptide mediators of cell proliferation including IL-1, TNF (87) and platelet-derived growth factor (PDGF) (88).
- 5) Increased formation and/or release of endothelium dependent relaxing factor (EDRF), i.e., NO (89).
- 6) Reduction in erythrocyte aggregation and deformability (90).
- 7) Reduction in endothelial-monocyte adhesion (reviewed in ref. 91).
- 8) ω -3 fatty acids in fish oil replace prostaglandin (PG)I₂ and PGA₂ with PGI₃ and PGA₃ favoring vasodilation and suppression of VSMC growth (72).
- 9) Conjugated linoleic acid reduces severity of atherosclerosis, reduces body fat, and enhances lean body mass (92).

Thus, there are a number of potential mechanisms by which PUFA are anti-atherosclerotic. However, in a group of selected patients with documented CAD, ω -3 PUFA, given for 2 years did not demonstrate an effect on slowing the progression of atherosclerosis of the carotid arteries as measured by ultrasound (93).

Monounsaturated Fatty Acids

The preventive effects of a monounsaturated fatty acid (MUFA)-rich diet on atherosclerosis may be explained by the enhancement of HDL-C levels and impairment of LDL-C levels, LDL susceptibility to oxidation, cellular oxidative stress, thrombogenicity, and atheroma plaque formation (reviewed in ref. 94).

Olive oil has an effect on lipid oxidation—inpatients with PAD, antioxidants present in extra virgin olive oil protect LDL against oxidation and decrease LDL uptake by macrophages compared to refined olive (95).

Olive oil has an effect on inflammation—olive oil decreases expression of VCAM-1 and interferes with activation of nuclear factor κ B (NF κ B) (96).

In rabbits, supplementing saturated fat diet with olive oil improved lipid profile, reduced vascular thrombogenicity and platelet activation with less severe morphological lesions of the endothelium and the vascular wall (97).

However, in Watanabe heritable hyperlipidemic (WHHL) rabbits, fish oil decreased blood lipids (cholesterol and triacylglycerol levels of intermediate density lipoprotein [IDL] and very low-density lipoprotein [VLDL]) and atherosclerosis compared with olive oil, although LDL oxidation was higher with fish oil (98). Also, depending on the underlying genotype, dietary MUFA and carbohydrates can actually increase atherosclerosis susceptibility (99).

Saturated Fats, Hydrogenated Fats/Trans–Polyunsaturated Fatty Acids, and Oxidized Fats

Postprandial hypertriglyceridemia increases oxidative stress and further deteriorates endothelial function even in patients with CAD (100). In humans, consumption of a diet high in hydrogenated fat increases production of inflammatory cytokines without affecting cellular immunity (101).

Oxidized fat and lipid oxidation products are present in human foods, are absorbed, and appear in blood circulation and can have deleterious CVD effects in humans (reviewed in ref. 102).

Paradoxically, linoleic acid, although an n-6 PUFA, has an atherogenic role through oxidative stress and cytokine mediated inflammatory response on the endothelium (reviewed in ref. 103). Corn oil (an n-6 PUFA source) increased oxidative stress and induced endothelial damage (104). On the other side, the incorporation of palm olein oil containing 38% palmitic acid, a saturated fatty acid, into a moderate fat, moderate cholesterol diet of nonhuman primate has antiatherogenic activity independent of cholesterolemic effects (105).

A high antioxidant vitamin status may help prevent the initiation and progression of early atherosclerotic lesion in man (106). Other dietary constituents that have an atheroprotective effect include low glycemic index, low-fat, high-protein diet (107), tomatoes (reviewed in refs. 108 and 109), and dietary soy isoflavone (110).

OBESITY

The role of obesity has been reviewed (111). Central fat distribution may contribute to atherogenesis, in part, because of associated alterations in insulin and lipoprotein levels (112), and because of the adverse effect on endothelium as suggested by the association of obesity with

increased vWF levels (113). Also, central obesity is associated with increased PAI-1 levels, increased fibrinogen levels, increased blood viscosity, and hypertension. It is also associated with increased uric acid levels through increased platelet aggregation and adhesion, increased blood viscosity, and propensity to coagulation (11). In a cross-sectional study, central fat mass in elderly women is associated with atherogenic tendencies and peripheral fat mass exhibits an independent dominant antiatherogenic effect (114). Fat cells from people with central adiposity have greater metabolic activity compared to normal cells. This is exemplified by an increase in lipolysis and release of free fatty acids (FFA) that may interfere with insulin clearance and exacerbate hypertriglyceridemia (115). Moreover, plasma insulin concentration inversely correlates with HDL-C and directly correlates with TG concentrations in plasma (116).

In a case control study, there was some trending supporting evidence that, in the absence of DM, homeostatic glycemic control (HbA1C) was a risk factor for atherosclerosis (117). Also, subjects from the general population with mild to moderate hyperglycemia following oral glucose load, but not in the fasting state, showed increased CVD risk (reviewed in ref. 118).

In men with atherogenic dyslipidemia of the insulin resistance syndrome, plasma C-reactive protein (CRP) levels showed positive correlations with body fat mass, waist girth, visceral adipose tissue, and insulin levels (measured in the fasting state and after a 75-g oral glucose load), but not with plasma lipoprotein levels (119).

However, in a cross-sectional study, insulin sensitivity and hyperinsulinemia did not play a role in femoral atherosclerosis, unlike lipid profile and BP in a follow-up setting (120).

ALCOHOL

Alcohol effects are mixed: in the Rottingham study (121) there was an inverse correlation between alcohol consumption and PAD in non-smoking men and women. In a prospective study, the association between regular alcohol intake and *early* atherosclerosis was J-shaped: the beneficial effects appeared to be through inhibition of the injurious actions of high levels of LDL-C. The association between regular alcohol intake and *advanced* atherosclerosis was U-shaped (122). The adverse and beneficial effects of alcohol on CVA are mediated by atherogenic and antiatherogenic properties. The relation between carotid artery disease and alcohol was U-shaped, approximately one-fourth of the atherosclerosis risk caused by severe alcohol consumption was mediated by

the risk profile associated with drinking, whereas the apparent beneficial effect of low alcohol intake emerged independent of conventional risk attributes (123). In female rabbits, alcohol intake representing 20 to 30%, but not 10%, of caloric intake increased VLDL and LDL, but not HDL, and decreased LDL receptor mRNA. It also increased lesion area and aortic cholesterols (124).

Red wine strongly inhibits ET-1 synthesis (125); phenolic acids in wine prevent LDL oxidation in the arterial wall (126), increases eNOS expression in HUVEC (127), inhibits PDGF- β receptor activation (128), and inhibits the proliferation and DNA synthesis in cultured rat VSMC (129). However, alcohol is a complementary component of phenolics in the benefits of red wine in hypercholesterolemic golden Syrian hamsters (130).

SMOKING

The role of smoking has been reviewed in ref. 131. Smoking has several contributing effects to atherosclerosis: in a prospective study, a direct association was found between atherosclerotic changes and number of cigarettes smoked per day. This risk was reduced, but not eliminated up to 10 years after cessation of smoking (132).

Even passive smoking has been shown to increase experimental atherosclerosis (133). Exposure of healthy nonsmoking subjects to passive smoking, in a follow-up study, caused an acute decrease in serum ascorbic acid levels and antioxidant defense, decreased LDL capacity to resist oxidation, increased serum levels of lipid peroxidation end products, and LDL isolated from these subjects was taken up by cultured macrophages at an increased rate (134). Secondhand smoke also caused endothelial dysfunction and increased adrenergic responsiveness (which was abolished by inhibition of NOS and removal of endothelium) and atherosclerosis in hypercholesterolemic rabbits. These effects were mitigated by L-arginine supplementation (135).

There is intersubject variability in cigarette-induced pathologies that is partly mediated by genetic variants, for example, eNOS intron 4 rare allele homozygotes are more likely to have myocardial infarction (MI) if they smoke (reviewed in ref. 136). Also, there is a synergistic effect between the Apo E allele epsilon 4 and smoking on carotid atherosclerosis in the Family Heart Study (137).

Smoking increased isolated blood monocytes adhesion to unstimulated HUVEC, mediated by integrin CD11b/CD18, along with decreased plasma vitamin C levels (138). In addition, the proathrogenic effect of cigarette smoking are mediated in part by the chronic infection found in smokers (139).

Both secondhand smoke and hypercholesterolemia were associated with significantly increased mitochondrial DNA damage, protein nitration, and increased atherosclerotic lesion formation (140).

HOMOCYSTEINE

The role of homocysteine (Hcy) in lipid oxidation has been addressed and reviewed (141). In males, moderate increase in Hcy levels in a case control study was an independent risk factor for cerebral infarction and MI and may predict the severity of the disease; levels were increased in 20 to 30% of patients with premature atherosclerosis. Also, in the presence of other traditional risk factors Hcy may have a permissive role in the endothelial damage even within the normal range, and this role may be related to free radical generating systems (142).

However, in a prospective study, atherosclerosis risk in communities (ARIC), there was doubt about a relation between CHD and Hcy and no association between CHD and C677T mutation of methylenetetrahydrofolate reductase gene or three mutations of cystathionine β -synthase gene. However, it was possible that vitamin B₆ offered an independent protection (143), and recently a review concluded that there is insufficient evidence to regard Hcy levels as a causative factor in atherosclerosis (144).

In Apo E null mice increased Hcy by a diet enriched with methionine but depleted in folate, B₆, and B₁₂ increased atherosclerotic lesion area and complexity and enhanced expression of receptor for advanced glycation endproducts (AGE), VCAM-1, TF, and MMP-9 in the vasculature. These effects were suppressed in parallel with decreased plasma Hcy levels upon dietary supplementation with folate, B₆, and B₁₂ (145). Also, methionine load increased vWF in patients with arterial or venous occlusive disease with or without hyperhomocysteinemia, suggesting endothelial dysfunction (146).

Hyperhomocysteinemia, in coronary arteries increased TNF- α expression, which enhanced oxidative stress ultimately impairing flow-induced dilation that can be reversed by superoxide dismutase (SOD) (147). Also, in EC Hcy inhibits dimethylarginine dimethylaminohydrolase (DDAH) enzyme activity by direct interaction (enzyme that degrades asymmetric dimethylarginine [ADMA]), causing ADMA to accumulate and inhibit NO synthesis, which might explain how Hcy impairs NO dependent vasodilation (148).

HUVEC converts Hcy to thiolactone (a byproduct of Hcy auto-oxidation). Folic acid inhibits this conversion; protein homocysteinylolation (indirect incorporation of Hcy into protein) increases with increasing

Hcy concentration and decreases with increasing folic acid and HDL in EC cultures. All this suggests a role in vascular disease (149). Hcy thiolactone combines with native LDL to form oxLDL, which is taken up by intimal macrophages to form foam cells (reviewed in ref. 150).

Hcy increased arterial SMC growth and collagen production. The addition of aquacobalamin controlled these effects (151). Diet-induced hyperhomocysteinemia in Apo E deficient mice promotes early atherosclerosis and plaque fibrosis, but does not weaken collagen or induce plaque rupture (152).

In human platelets, Hcy diminished NO production through decreased uptake of L-arginine without any effect in NOS activity (153).

INFLAMMATION

Inflammation and its mediators have received a lot of attention as a contributing factor to atherosclerosis.

In 81-year-old subjects, high plasma TNF- α was associated with atherosclerosis but not with TC, LDL, and BMI, and was weakly correlated with TG, leukocytes, CRP, and low HDL/TC ratio (154). The presence of antinuclear antibodies is substantially more prevalent among subjects with severe coronary atherosclerosis than those with normal coronary arteries (155). On the other hand, in a double-blind randomized placebo controlled cross over trial of healthy men, acute systemic inflammation augmented local forearm tPA release suggesting it can invoke a protective response (156).

Cell Adhesion/Chemotaxis

Leukocyte count is associated with aortic arch plaque thickness, and is specifically correlated with aortic arch plaque thickness equal to or more than 4 mm in stroke-free subjects (157). In WHHL rabbits, leukocyte adherence to intact arterial endothelium is one of the genes and promoters of atherosclerosis (158).

Chemokines contribute to leukocyte recruitment, angiogenesis, and proliferation and migration of SMC into atherosclerotic plaques; in addition, leukocytes and EC are an important source of chemokines and many atherosclerotic risk factors increase chemokine expression. Furthermore, interactions between cells such as leukocytes and EC amplify chemokine release that may contribute to sustained chemokine generation in inflammatory conditions (reviewed in ref. 159). Fractalkine (FK; now also called CX3CL1) is a unique chemokine that functions not only as a soluble chemo-attractant but also as a transmembrane-anchored adhesion receptor, and is expressed on activated ECs. The fractalkine

receptor, CX3CR1, is expressed on cytotoxic effector lymphocytes, including natural killer (NK) cells and cytotoxic T-lymphocytes and on macrophages. Soluble fractalkine causes migration of NK cells, cytotoxic T-lymphocytes, and macrophages, whereas the membrane-bound form captures and enhances the subsequent migration of these cells in response to secondary stimulation with other chemokines. Furthermore, stimulation through membrane-bound fractalkine activates NK cells, leading to increased cytotoxicity and interferon- γ production (reviewed in ref. 160). CX3CR1 $-/-$ mice have a significant reduction in macrophage recruitment to the vessel wall and decreased atherosclerotic lesion formation (161).

oxLDL, but not LDL, upregulates CXCR2 expression in monocytes and promotes the chemotaxis and adhesion of monocytes (162).

E- and P-Selectins, play important roles in early and advanced stages of atherosclerosis: in E- and P-selectin double (LDL receptor deficient) KO mice on an atherogenic diet, lesions were smaller but contained the same number of macrophages than control animals (LDL receptor deficient) (163).

MCP-1 and chemokine receptor 2 (CCR2) play important roles in monocyte recruitment: MCP-1 expression is increased in human atherosclerotic plaques, vascular endothelium, and VSMC exposed to minimally modified lipids. In Apo E deficient mice that lack CCR2, lesion formation was decreased with no effects on lipids (164); on the other hand, MCP-1 expression by leukocytes (macrophages) increases macrophage number and oxidized lipid accumulation and atherosclerosis progression in Apo E deficient MCP-1 transgenic mice, with no effects on plasma lipoprotein profile (165). However, local MCP-1 overexpression at the vessel is not sufficient in rabbits, and activation by other factors induced by hypercholesterolemia is required (166).

ICAM-1 and lymphocyte function-associated protein (LFA)-1 pathway are involved in monocyte-endothelium interaction during a cholesterol-rich diet. In rats on high-cholesterol diet, ICAM-1 expression was increased on aortic EC, which was associated with increased monocyte adherence (more than 85% of adherent macrophages exhibited LFA-1 antigen and injecting the animals with ICAM-1 monoclonal antibody and LFA-1 monoclonal antibody reduced mostly LFA-1 positive macrophages) (167). In clinically healthy middle-aged men, levels of soluble ICAM-1 (sICAM-1), but not sVCAM-1 or E-selectin, were associated with subclinical atherosclerosis and inflammatory variables (168).

TNF- α is produced by macrophages and promotes inflammatory reactions, including induction of vascular adhesion molecules and

macrophage recruitment and proliferation. However, in mice TNF receptor p55 protects against atherosclerosis because its absence was associated with increased scavenger receptor activity (169). Additionally, in individuals younger than 70 years of age in a multi-ethnic urban population, relative elevation of TNF receptor levels, but not TNF levels, was associated with carotid atherosclerosis (170).

Monocyte Activation

The role of monocytes has been reviewed in ref. 171; Neopterin, a marker of macrophage activation, was higher in patients with unstable angina compared with patients with stable angina independent of *C. pneumoniae* seropositivity (172).

The interaction of monocyte with nonenzymatically glycosylated matrix protein in the vessel wall may result in a faster rate of induction of monocyte/macrophage (M/M) differentiation leading to foam cell formation (173). During the initiation of lesion development, foam cells derive mainly from circulating precursors rather than resident macrophages (174). Macrophages in humans induce human VSMC apoptosis ultimately promoting directly plaque rupture (175). Cyclo-oxygenase (COX)-2 is upregulated in activated M/M, LDL receptor $-/-$ mice null for macrophage COX-2 developed less atherosclerosis than LDL receptor $-/-$ mice, even though COX-2 contributes to the production of prostacyclin (reviewed in ref. 176).

Immune Reactions

Immune reactions can modulate atherosclerosis development (reviewed in ref. 177); nonspecific stimulation of the innate immune system by endotoxin accelerates cholesterol-induced atherosclerosis in rabbits (178).

Complement components have been isolated from lesions and lesion severity is decreased in complement-deficient animals; complement-mediated release of MCP-1 from human VSMC may be important in monocyte recruitment (179).

Increased auto-antibodies against oxLDL was associated with CAD (180). In Apo E deficient mice, lipopolysaccharide (LPS) injection caused an increase in antibodies against oxLDL, an increase in atherosclerotic lesion size, and increased IL-4-producing NK T cells (181). Anti-phosphorylcholine (PC) antibodies have reactivity against oxLDL and other oxidation-specific structures containing PC antigen; cells undergoing apoptosis express a range of oxidation-specific neoself PC determinant (182). However, in another study there was no significant association between circulating antibody titers to malondialdehyde-modified (MDA)-LDL and coronary atherosclerosis (183). Human-

derived anti-oxLDL auto-antibody blocks oxLDL uptake by macrophages and localizes to atherosclerotic lesions in vivo (184). In Apo E knockout (KO) mice, splenectomy aggravated atherosclerosis, and transfer of spleen cells reduced disease development (specifically B-cells). This protection was demonstrated on nonsplenectomized mice, and was associated with an increase in antibodies to oxLDL. In protected mice, few CD4+ T-cells were found. Therefore, it is suggested that B-cell associated protective immunity develop during atherosclerosis and reduces disease progression (185).

Elevated IgA anti- β 2-glycoprotein 1 (an antigen of autoimmune anticardiolipin antibodies) and IgG antiheat shock protein (Hsp) 60/65 antibodies are associated with increased risk of ischemic stroke independent of other risk factors (186). The antigen-antibody complex target oxLDL, so the complexes are involved in oxLDL uptake into macrophages (reviewed in ref. 187).

Other Inflammatory Mediators

In vitro studies demonstrated that ligation of the immune mediator, CD40, on atheroma-associated cell types mediates expression of cytokines, chemokines, growth factors, MMPs, and procoagulants (reviewed in ref. 188). CD40 and CD40 ligand are expressed in cells in atherosclerotic lesions: in LDL receptor deficient hypercholesterolemic mice, CD40 ligand antibody limited atherosclerotic lesions with less lipid content, fewer macrophage and T-lymphocytes, and decreased VCAM-1 expression in the lesions (189).

Interferon- γ can induce arteriosclerotic changes in the absence of immunocytes by potentiating VSMC mitogenesis (190). In Apo E $-/-$ mice, interferon- γ deficiency decreased atherosclerosis, in males only, by decreasing T-lymphocyte presence and cell activation without influencing serum cholesterol concentration (191).

The expression of proinflammatory ILs and their receptors has been demonstrated in atheromatous tissue, and serum levels of several ILs have been found to correlate positively with arterial coronary disease. Several ILs have been involved in vitro with upregulation of adhesion molecules on EC, activation of macrophages, and SMC proliferation. Some ILs are proatherogenic and others are anti-atherogenic (reviewed in ref. 192).

Factors secreted by adipose tissue especially visceral adipose tissue (adipokines) increase with increased adiposity and regulate a number of factors that contribute to the development of atherosclerosis (reviewed in ref. 193).

Synthetic peroxisome proliferator-activated receptors (PPARs) agonist in clinical use such as thiazolidinediones (TZDs) may limit inflammatory response (194). Also, PPAR γ , but not PPAR α , activators repress interferon- γ -induced MHC-II expression and subsequent inhibition of T-lymphocyte activation in atheroma-associated cells (195).

The role of atherogenic lipoproteins on inflammation has been reviewed in ref. 196. PAF (a proinflammatory phospholipid) metabolism is independent of cellular cholesterol content, and foam cells and macrophages produce transiently PAF upon phagocytosis at inflammatory sites in intima (197). On the other hand, in HUVEC Apo E, secreted locally at lesion sites by macrophages may be anti-inflammatory (198).

Given the lipoprotein binding and complement activation of CRP (an acute phase response protein) and its localization in atherosclerotic vessels, there is a strong likelihood that CRP may be involved in the atherosclerotic process (reviewed in ref. 199). Human coronary artery SMCs, but not HUVECs, could produce CRP in response to inflammatory cytokines (200). In human saphenous vein EC, CRP increases ET-1 and IL-6 production leading to increased MCP-1 production and native LDL uptake by macrophages (201). In human aortic endothelial cells (HAEC), CRP induced PAI-1 expression and activity (202); CRP may contribute to foam cell formation in atherosclerotic lesion by causing the aggregation of LDL molecules that are then taken up by macrophages (203). However, CRP level was not related to the extent or presence of coronary atherosclerosis in another study (204).

The role of NF κ B has been reviewed in ref. 205. NF κ B is a key regulator of inflammation, immune responses, cell survival, and cell proliferation; inhibition of the NF κ B pathway in macrophages leads to more severe atherosclerosis in low density lipoprotein receptor (LDLR) deficient mice, possibly by affecting the pro- and anti-inflammatory balance that controls the development of atherosclerosis (reduced production of LPS-stimulated TNF, and reduction in IL-10) (206).

Endothelin-converting enzyme (ECE)-1 activates ET-1, both are abundantly present in human arteries and at different stages of atherosclerotic plaque evolution. The upregulation of the ECE-1/ET-1 system is closely linked to the presence of chronic inflammation and is present in very early stages of plaque evolution (207). ET system is upregulated by LDL and oxLDL in cultured human coronary SMC and human monocyte-derived macrophages (208).

Also, dendritic cells (DC) accumulate in atherosclerotic lesions (reviewed in ref. 209); oxLDL can activate DC but high concentrations increase DC apoptosis (210). Direct contact between activated DC that

over-express HSP70 and T-cells might be responsible for T-cell activation, and might facilitate the presentation of lipid antigen to T-cells directly within the human arterial wall in early intimal lesions (211).

INFECTIONS

The first inflammatory stage of atherosclerosis starts early in life with more severe lesions developing only if classical risk factors, especially cholesterol, remain present. Immune responses mounted against antigens cross-react with homologous host proteins in a form of molecular mimicry, for example, HSP are secreted by *C. pneumoniae*, *H. pylori*, mammalian vascular cells exposed to stress such as CVD risk factors, and cells within atherosclerotic plaques. In addition, serum titers of anti-HSP antibodies are correlated positively with the future risk of CHD, and purified anti-HSP antibodies lyse stressed human EC and macrophages in vitro. Furthermore, immunization with HSP exacerbate atherosclerosis in animal models (reviewed in refs. 212,213). However, there is molecular mimicry between epitopes of oxLDL and *Streptococcus pneumoniae* in LDLR $-/-$ mice: pneumococcal immunization led to increased IgM levels against oxLDL and decreased the extent of atherosclerosis (214).

Risk factors for atherosclerosis evoke HSP over-expression on EC, macrophage, and SMC; HSP could be a soluble factor in the blood, which is positively correlated with atherosclerosis in humans (normally it is localized intracellularly). Soluble HSP binds to the toll-like receptor (TLR)-4/CD14 complex initiating an immune response, including the production of pro-inflammatory cytokines by macrophages and adhesion molecules in EC via NF κ B activation. Titers of HSP antibodies are increased in patients with atherosclerosis, and T-lymphocytes specifically responding to HSP have been found in atherosclerotic plaques (reviewed in ref. 215). In addition, TLR-4, the receptor for bacterial LPS, recognizes cellular fibronectin and HSP 60 and is expressed in human adventitial fibroblasts and macrophages, the activation of adventitial TLR-4 augmented neointima formation in a mouse model (216). Also, pro-inflammatory bacterial peptidoglycan (a functional LPS analog) and its co-receptor, toll-like receptor-2, have been observed in atherosclerotic arteries in association with the vulnerable plaque phenotype (217). Pathogens interfere with macrophage cholesterol metabolism through inhibition of the liver X receptors (LXR) signaling pathway: activation of TLR 3 and 4 by microbial ligands blocks the induction of LXR target genes including ATP-binding cassette transporter class A1 (ABCA1) in cultured macrophages, as well as in aortic tissue in vivo. As

a consequence of these transcriptional effects, TLR3/4 ligands strongly inhibit cholesterol efflux from macrophages (218).

The pronounced expression of IL-6 and IL-8 by virus-infected monocytes may induce local or systemic inflammation, which may be associated with plaque rupture. These processes may be accelerated by the lack of the production of the anti-inflammatory cytokine IL-10 (219).

In vitro and animal model studies have suggested that infectious agents and their products can activate the coagulation cascade enzymatically or by upregulating TF. Alternatively, some microbes can directly trigger platelet aggregation (reviewed in ref. 220).

The role of *C. pneumoniae* has been reviewed in ref. 221. Also, there is a significant association between infectious burden and the extent of atherosclerosis (222); the IgG antibody response to multiple pathogens is an independent risk factor for endothelial dysfunction and the presence and severity of CVD (223).

PATHOLOGY OF ATHEROMA

The atherosclerotic process begins, according to the response-to-injury-hypothesis, with a structural or functional injury to the endothelium resulting in increased permeability of the endothelial barrier to blood cells, hormones, and lipoproteins (224–226). The elastic lamina, secreted by and subjacent to endothelium, provides a barrier to the entry of macromolecules and cells and its absence is associated with atherosclerosis (227). Platelets aggregate at the site of injury and release growth factors and chemo-attractants that subsequently stimulate proliferation of VSMC. Migration of these cells and macrophages to the subintimal region subsequently occurs, the place where the atherosclerotic process develops (11,224–226).

Half the infants in the first 6 months of life have foam cells in susceptible segments of the coronary arteries. Later on, fewer children have them, but at puberty they accumulate and preatheromas develop and contain lipid droplets and dead cell remnants (extracellular lipids) and macrophages (228). Atheromas have a lipid core in which increased extracellular lipids displace SMC and ECM and then calcium granules appear in some SMCs and among the extracellular lipid of the core, lipid core and inflammation may be an underlying cause of lesion rupture, which makes intervention important at this young age (228).

This lipid core incites inflammation and in conjunction with the thin fibrous cap this constitutes a vulnerable plaque, rupture of such vulnerable plaques account for the majority of CHD death, particularly sudden death. The early reduction with CHD death with HMG-CoA reductase

inhibitors is caused by a reduction in lipid core (229). Large necrotic cores, fibrous caps $< 65 \mu$, and numerous macrophages within the cap likely indicate instability and rupture of thin cap atheromas. Speckled pattern of calcification predicts vulnerability to rupture (reviewed in ref. 230). Coronary artery plaques with positive remodeling (outward expansion of the vessel wall) have a higher lipid content and macrophage count, both markers of plaque vulnerability compared with lesions with negative remodeling (vessel shrinkage). These results may explain why plaque rupture is often apparent at sites with only modest luminal stenoses (but marked positive remodeling) (231). Also, hemodynamic forces may play a crucial role in the pathogenesis of plaque disruption (232). Plaques that develop into end-stage *culprit plaques* are distinct from *stable plaques* by location and early lesion morphology, suggesting distinct lesion development and progression pathways; also, poly-genic hypertension accelerates coronary plaque progression and complication (233).

The atherosclerotic process changes the cellular responsiveness and function of the vessel as a result of changes in VSMCs (reviewed in ref. 234) This can be understood by knowing the phenotypic make-up of the VSMC. There are two major phenotypes of arterial VSMCs (224,225): (1) the *contractile phenotype* found in arterial media and made up of myofilaments; it is responsible for contraction and relaxation of the vasculature; and (2) the *synthetic VSMC* phenotype, which is found in the intima during the atherosclerotic process following the migration of contractile VSMC from the media.

Several factors are considered important in the transformation to a synthetic phenotype:

1. Fas ligand expression increased SMC in intima leading to acceleration of atherosclerotic lesion growth (235).
2. Calcium deficiency in chick embryos accelerates cell proliferation, decelerates sarcomeric protein expression in vitro, and induces atherosclerosis (236).
3. LDL acts as a growth factor promoting VSMC growth (reviewed in ref. 237).
4. Lp(a), in transgenic rabbits, promotes SMC proliferation and dedifferentiation possibly because of impaired fibrinolytic activity (238).
5. Unsaturated lysophosphatic acid (LPA), but not saturated LPA, specifically induces VSMC differentiation (239).
6. In a rat SMC line, overexpression of LR 11, a member of LDL receptor family and highly expressed by VSMC of hyperplastic intima but not media, induced enhanced migration and invasion activities of intimal SMCs in vitro (240).

7. gp38k (CHI3L1) is a secreted heparin-binding glycoprotein whose expression *in vitro* is associated with VSMC migration and invasion into the underlying gelatinous matrix (241).
8. Activator protein (AP)-1 activation is crucial for the mediation of VSMC proliferation in response to balloon injury to the rat carotid artery (242).
9. Activation of extracellular signal-regulated kinases (ERKs), protein kinase C, tyrosine kinase, and p38 MAPK is essential for pressure-induced DNA synthesis in rat VSMC (243).
10. The demonstration of microsatellite instability and loss of heterozygosity in SMCs of human plaques suggests that genomic destabilization may play a pivotal role in atherosclerotic mechanisms. Furthermore, the use of accepted biomarkers of carcinogenic exposure—such as DNA adducts and cytogenetic endpoints—recently has provided evidence consistent with the view that somatic cell alterations are critical in atherogenic process (reviewed in ref. 244).
11. SMCs develop hypomethylation *in vitro* during transformation from a contractile to a synthetic phenotype. Genomic hypomethylation occurs during atherogenesis in human, mouse, and rabbit lesions, and it correlates with increased transcriptional activity. Also, methyltransferase is expressed in atherosclerotic lesion and hypomethylation is present in advanced lesions and may reflect cellular proliferation and gene expression in atherosclerotic lesions (245).
12. Extracellular uridine 5'-triphosphate (UTP) induces mitogenic activation of SMCs through binding to P2Y2 nucleotide receptors. P2Y2 receptor mRNA is upregulated in intimal lesions of rat aorta, and has a role in the development of intimal hyperplasia in collared rabbit carotid artery (246).
13. Polyamines such as putrescine, spermidine, and spermine are involved in the transition of migrated VSMC into a synthetic phenotype (226).
14. Smooth muscle associated protein 2 was upregulated during neointima formation in a rat carotid endarterectomy model (247).

On the other hand, other factors are important in establishing the contractile phenotype:

1. The expression of the major receptor protein for NO signaling in smooth muscle, cGMP-dependent protein kinase, is important to establish contractility in rat aortic SMC in culture (248).
2. The natriuretic peptides (NPs), atrial natriuretic factor (ANF), and B and C type NPs (BNP and CNP) have potent antiproliferative and antimigratory effects on VSMCs. NPs and their receptors (NPRs) mRNAs are present in human coronary arteries (249).
3. The TR3 orphan receptor, the mitogen-induced nuclear orphan receptor (MINOR), and the nuclear receptor of T-cells (NOT) are a subfamily of

transcription factors belonging to the nuclear receptor superfamily, and are induced in activated SMCs. There is expression of TR3, MINOR, and NOT in neointimal SMCs, whereas there is no expression detected in medial SMCs; TR3 orphan receptor inhibits SMC proliferation and vascular lesion formation (250).

These synthetic cells proliferate, take up LDL-C and synthesize abnormally large amounts of collagen, elastin, and proteoglycans (225,226). Hypoxia increases LDL uptake and enhances lipid accumulation in arterial SMC (251). Thus, VSMC that are contractile in the media become phenotypically different upon migrating to the intima.

Human aortic SMC gained macrophage scavenger receptor and macrophage phenotype supporting possible transformation of SMC into foam cells: CD36 is a scavenger receptor class B for oxLDL and plays an important role in foam cell formation from monocytes (reviewed in ref. 252). PPAR γ was expressed in CD 36 positive cells, PPAR γ ligand upregulated CD36 expression in CD36 positive cells only (253); absence of CD36, in an atherogenic Apo E null background, resulted in a 70% decrease in total lesion area in western diet-fed mice. oxLDL can stimulate its own uptake by induction of CD36 gene expression that involved activation of PPAR γ (reviewed in ref. 254).

Bone marrow cells have the potential to give rise to vascular progenitor cells that hone in on damaged vessels and differentiate into SMC and EC (255) However, progressive progenitor cell deficits, the effect of concomitant vascular aging, may contribute to the development of atherosclerosis (256), because the age-dependent failure of the bone marrow to produce vascular progenitor cells responsible for arterial repair drives atherosclerosis and its thromboembolic complications (reviewed in ref. 257).

GROWTH FACTORS, CYTOKINES, AND MITOGENESIS

A number of mitogens play an important role in the atherosclerotic process (258). Table 2 summarizes some of the more important mitogens implicated in the atherosclerotic process. The contribution of each factor will be briefly discussed in the context of the atherosclerotic process.

Angiotensin II

AII has the following effects:

1. In Apo E-deficient mice, AII stimulates macrophage cholesterol biosynthesis through AT1 receptor followed by induction of HMG CoA

Table 2
Some Mitogens and Cytokines Associated With Development of Atherosclerosis

Platelet derived growth factor
Insulin-like growth factors
Epidermal growth factor
Transformation growth factor- β
Fibroblast growth factor
Interleukin-1
Endothelin-1
Tumor necrosis factor- α
MCP-1
VMAP-1
Selectins
ICAM-1
VCAM-1
LFA-1
CD40 and CD40L
ECM (heparan sulfate)
Tissue factor
PAI-1
vWF
VEGF

reductase gene expression, inhibition of AII activity attenuate atherosclerosis (259).

2. In mouse peritoneal macrophages, AII atherogenicity may be related, at least in part, to its inhibitory effect on macrophage cholesterol efflux mediated through AT1 and not the ABC1 transporter, thus leading to cellular cholesterol accumulation (260).
3. AII stimulates macrophage uptake of oxLDL, mediated by IL-6 in Apo E deficient mice (261).
4. AII inhibits insulin signaling through AT1 receptor and bradykinins/NO dependent blood flow (11).
5. AII stimulates expression of platelet-derived growth factor (PDGF)-A chain mRNA and secretion of PDGF-like molecules, and vascular SMC hypertrophy (262).
6. AII activates nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enhancing SMC growth and proliferation, stimulating inflammatory proteins, and modulating matrix remodeling (263).
7. AII, through activation of NF- κ B-mediated pro-inflammatory genes, promotes vascular inflammation, leading to acceleration of atherosclerosis.

rosis and induction of aneurysm in Apo E-KO mice. Downregulation of PPAR- α and - γ by AII may diminish the anti-inflammatory potential of PPARs, thus contributing to enhanced vascular inflammation (264).

8. In Apo E-KO mice, AII treatment accelerated atherosclerosis in the carotid artery, increased blood pressure, increased arterial stiffening, increased pulse wave velocity, and decreased arterial elasticity. These functional changes were correlated with morphological and biochemical changes as demonstrated by an increase in collagen content, a decrease in elastin content, and breaks in the internal elastic lamina in the aortic wall. In addition, endothelium-independent vasorelaxation to sodium nitroprusside was impaired (265).
9. MMPs have no role in AII-induced atherosclerosis but MMPs have a role in AII-induced abdominal aortic aneurysm (AAA) formation in mice (266).

AT1 receptor is responsible for most of the pathophysiologic actions of AII. Estrogen deficiency and hypercholesterolemia increases AT1 receptor expression. Both AT1 receptor antagonist and ACE inhibitors improve endothelial dysfunction; AT2 causes antiproliferation and counteracts the cell growth induced by AT1 activation (reviewed in refs. 267 and 268). Hypoxia and hyperglycemia upregulates AT(1) receptor expression in cultured VSMC, suggesting a mechanism for enhanced AII-induced VSMC proliferation and the development of atherosclerosis in diabetes (269). Whereas antagonism of AT1 receptors totally prevented the formation of aneurysms, antagonism of AT2 receptors promoted a large increase in the severity of AII-induced vascular pathology with no change in plasma lipid concentrations and only transient and modest increases in blood pressure (270).

Also, mineralocorticoid receptor antagonism improves endothelial function and reduces O₂^{*}-generation in diet-induced atherosclerosis (271). In Apo E $-/-$ mice, administration of the selective aldosterone blocker, eplerenone, significantly reduced oxidative stress and atherosclerosis progression (272).

In rabbits, vascular ACE activity was significantly increased by atherogenic diet with significant correlation between vascular ACE activity and plaque area, however, contractile responses of the femoral arteries to AI and AII in the atherogenic diet-fed animals were not different from those of the normal diet-fed animals (273). ACE inhibition improves vascular compliance, NO production, vascular relaxation, plasma markers of relaxation, oxidative stress, and thrombosis (reviewed in ref. 274). On the other hand, hypercholesterolemia in rabbits resulted in atherosclerosis, loss of endothelium-dependent relaxation, increased AT1 in aortic tissues with enhanced constrictor response to AII (275).

Platelet-Derived Growth Factor

PDGF may also interact with other growth factors, such as IGF-I to enhance VSMC proliferation and migration (276). Infusion of PDGF into rats subjected to carotid injury produces a two- to threefold increase in medial VSMC proliferation, but a 20-fold increase in intimal thickening and VSMC migration from media to intima within a week following injury (277). However, in Apo E null mice elimination of PDGF- β from circulating cells or blockade of PDGF receptors transiently delays, but does not appear sufficient to prevent smooth muscle accumulation in advanced lesions of atherosclerosis (278).

VSMCs isolated from intimal lesions after balloon catheterization synthesize significantly greater amounts of PDGF than VSMC isolated from normal media. PDGF receptor activity also increases when VSMC change to a synthetic phenotype. Both PDGF and epidermal growth factor (EGF) then interact to further promote migration of VSMC to the intima and subsequent proliferation of these migrated cells (279). Also, PDGF- β is capable of inducing MMP-3 expression (280).

IGF-I, IGF-II and insulin appear to have an important role in the pathogenesis of atherosclerosis (281). IGF-I has been shown to stimulate 3H thymidine incorporation by VSMC. IGF-I is an autocrine/paracrine peptide, which is produced by VSMC and cardiomyocytes under the control of stretch, AII, PDGF, and growth hormone (GH) (282,283). Arterial injury is accompanied by a rapid and long lasting induction of VSMC IGF-I mRNA expression (281). EC produce IGFs, and EC dysfunction may lead to increased release of IGFs, which, in turn, may promote neointimal VSMC proliferation (281). They also stimulate proliferation of EC (281); and IGF-I promotes vascular inflammation in EC by potentiating c-jun and NF κ B activation by TNF- α and enhancing TNF- α -mediated adhesion molecule expression (284).

Platelets express both IGF-I, and IGF-II, the expression being localized to the α -granules. Platelets also have IGF-I receptors, and platelet adherence and degranulation (activation) leads to the release of IGF (281). Macrophage precursors also have IGF-I receptors and IGF stimulates the proliferation of these cells and their conversion into multinucleated cells (281). VSMC express receptors for IGF-I, IGF-II, and insulin (281,285). PDGF and IGF-I have synergistic effects on expression of the proto-oncogene *c-myc* in cultured bovine VSMC and in promoting cell growth (281). Although insulin does not increase the mitogenic effect of IGF-I, the mitogenic response of insulin is mediated, in part, through an IGF-I receptor (281). Insulin has been shown to increase IGF gene expression in aortic VSMC (281). Further, in insulin-deficient diabetic

rats, aortic IGF-I mRNA abundance is significantly reduced compared to that in nondiabetic rats (285). Infusions of insulin into the aorta resulted in a twofold increase in IGF-I mRNA in aorta indicating that hyperinsulinemia might play its role in atherogenesis, in part, through enhanced expression of IGF-I in vessel wall (285).

Insulin alone or with PDGF does not appear to have a significant effect on VSMC migration (285,286). However, VSMC migration induced by the cyclooxygenase product 12-HETE is increased in relation to the concentration and duration of exposure to insulin (287); this effect is augmented by increasing glucose concentration (286).

IGFs, lipoproteins, and insulin are abundant in plasma under normal conditions. Thus, it is possible that these factors are also important in vivo (11,286,288,289); this concept was examined by taking platelet extract from humans and exposing it to rat aortic VSMCs. It caused proliferation of these cells, an effect that was more pronounced when the extract from diabetic vs normal subjects was used (290). Moreover, this increased proliferative effect by the platelet extract from diabetic patients was markedly reduced after treatment to normalize plasma glucose. This adds further support to the notion that either hyperosmolarity or some factor other than insulin contributes to the development of the atherosclerotic process. The AGE-receptor for AGE interaction in VSMC, in addition to growth factors induced by AGE, contributes to the stimulatory effects of diabetic sera on VSMC proliferation that can accelerate atherosclerosis (291).

However, several studies in nondiabetics suggest that lowered circulating IGF-I levels account for a poor outcome of CVD. Also, genetically determined lowered IGF-I levels increase the risk of MI with type 2 DM. It is possible that the premature and progressive decline in serum IGF-I bioactivity in ageing patients with type 2 DM is an important pathophysiological abnormality because it contributes to elevated glucose and lipid levels and the progression and poor outcome of CVD (reviewed in ref. 292). Individuals without ischemic heart disease (IHD) but with low circulating IGF-I levels and high IGF binding protein (BP)-3 levels have significantly increased risk of developing IHD during a 15-year follow-up period (293).

Homozygosity for a disrupted IGF-II allele in mice lacking apolipoprotein E results in aortic lesions that are approximately 80% smaller and contain approximately 50% less proliferating cells compared with mice lacking only apolipoprotein E; and targeted expression of an IGF-II transgene in SMC, but not the mere elevation of circulating levels of the peptide, causes per se aortic focal intimal thickenings. These observa-

tions provide a direct evidence for an atherogenic activity of IGF-II in vivo (294).

Epidermal Growth Factor

EGF has been shown to be secreted by platelets, and to stimulate proliferation of VSMC in culture (262). The mitogenic effects of EGF are calcium dependent and are similar to other mitogens such as IGF-I (262). The VSMC proliferative effects of EGF are potentiated by insulin, suggesting that factors such as hypertension and hyperinsulinemia may be synergistic in promoting the atherogenic process.

Heparin-binding EGF-like growth factor (HB-EGF), produced locally by vascular macrophages and SMCs, has been suggested to induce the migration and proliferation of VSMCs. HB-EGF mRNA is abundantly expressed in human adipose tissue. Also, plasma HB-EGF levels increase in parallel with fat accumulation in humans, and the subjects with CAD have higher plasma HB-EGF levels, associated with fat accumulation (295).

Transforming Growth Factor β

Transforming growth factor (TGF)- β is produced by many cells including VSMC (296), EC (296), macrophages (297), T-lymphocytes (296), and platelets (298). Thus, it may have a modulatory role in the atherosclerotic process. Inhibition of TGF- β signaling accelerates the development of atherosclerotic lesion in Apo E deficient mice, and favors the development of lesions with increased inflammatory component and decreased collagen content (299). However, in another study that was associated with a decrease in plaque area (300), TGF- β has been shown to decrease proliferation of VSMCs despite induction of cellular hypertrophy (301). However, TGF- β can stimulate VSMC growth (225). Also, native LDL can stimulate SMC proliferation with increased protein kinase C activity (both are inhibited by α -tocopherol through a mechanism unrelated to its radical scavenging properties) through inhibition of TGF- β secretion by SMC; α -tocopherol increases TGF- β release (302). Its net effect on VSMC growth depends, in part, on its ability to stimulate formation of appropriate ECM proteins (225,296). TGF- β stimulates expression of PDGF-A chain mRNA and secretion of PDGF-like molecules (279); Thus, TGF- β has a regulatory role rather than an initiating role of primary events.

Fibroblast growth factors (FGF) type 1 and 2 are expressed in EC and VSMC (225,303). FGF plays an important role in control of VSMC replication whenever cell injury has occurred (225). FGF stimulates growth in quiescent VSMC in culture (225).

ET-1 also acts as a growth factor for VSMC. This effect is more pronounced in the presence of insulin (304,305). Norepinephrine and histamine increase EC proliferation and increase VSMC proliferation and migration (262). Epinephrine also stimulates proliferation of VSMC and α agonists stimulate PDGF-A chain gene expression (262).

Cytokines such as IL-1 and TNF- α are produced by macrophages (306,307). Both of these cytokines inhibit EC growth and stimulate VSMC growth, the opposite mitogenic effects correlate with reduction and increase in FGF receptor number displayed by EC and SMC, respectively (308). However, TNF- α markedly decreased IGF-I mRNA and increased IGFBP-3 mRNA and protein in rat aortic VSMCs leading to a reduction in bioactive IGF-I thereby decreasing VSMC viability and promoting plaque instability; whereas IGF-I prevents apoptosis, promotes matrix formation, and can decrease TNF- α and IL-1 β -induced proteoglycan degradation (309). Also, IL-1 promotes growth of VSMC via induction of synthesis of PDGF with no effect on intracellular Ca²⁺ (310).

Another cytokine, IL-6, induces an increase in VSMC thymidine uptake and proliferation (311). IL-6 also stimulates PDGF production and the VSMC proliferative effects of this cytokine are inhibited by PDGF antibody (as measured by thymidine uptake) (311). These results indicate that IL-6 has an autocrine function through stimulation of PDGF production (311).

Another cytokine, smooth muscle-derived growth factor (SDGF), has been shown to be distinct from competent and progression growth factors and to stimulate different pathways in VSMC (312). Thus, cytokines have a profound and complex effect on VSMC proliferation, and thus the atherogenic process.

Stress and the Sympathetic Nervous System

In the ARIC study, clinical atherosclerosis was associated with low income and low education (313). Also, there was a correlation between cerebrovascular disease and anger and aggression (314). Chronic psychological risk factors (hostility and low socioeconomic factors) are important at early disease stages. Episodic factors (depression and exhaustion) are involved in the transition from stable to unstable atherosclerotic plaques, and acute psychological triggers (mental stress and anger) can promote myocardial ischemia and plaque rupture (reviewed in ref. 315). It has been proposed that postprandial insulin resistance along with increased levels of cortisol and catecholamines, specifically

stress, play a major role in the development of early occlusive atherosclerosis (reviewed in ref. 316).

Stress induced a heightened state of CVD reactivity, injured endothelium and induction of adhesion molecules on EC to which recruited inflammatory cells adhere and translocate to the arterial wall. An acute phase response is also engendered and stress induces an atherosclerotic lipid profile with oxidation of lipids and, if chronic, a hypercoagulable state (reviewed in ref. 317). The prolonged endothelial dysfunction induced by mental stress is prevented by selective endothelin-A receptor antagonism (318), whereas leisure time physical activity had a positive effect and TV watching time a negative effect on HDL, BMI, waist girth, waist-hip ratio, and subscapular and triceps skinfold thickness (the reverse effect on TG) but not with carotid artery IMT (319).

Sex Hormones Effects

Sex hormones have different influences on atherosclerosis (reviewed in ref. 320). The incidence of CHD in women younger than 55 years of age is one-third that of men, but becomes closer to that of men by age 75. Also, mortality from CHD is higher in women. In summary, estrogens have the following effects: inhibition of L-type calcium currents, increased HDL, decreased LDL, decreased LDL oxidation, decreased VSMC growth, and increased NO production by platelets, EC, VSMC, and myocardiocytes (reviewed in ref. 321). The presence of CAD in postmenopausal women is independently associated with altered cholesterol metabolism, as reflected by low synthesis and inefficient elimination of cholesterol (322). Also, among premenopausal women undergoing coronary angiography for suspected myocardial ischemia, disruption of ovulatory cycling characterized by hypoestrogenemia of hypothalamic origin appears to be associated with angiographic CAD (323).

Postmenopausal hormone replacement therapy (HRT) is associated with lower total number of atherosclerotic plaques and less severe atherosclerotic lesions, which may be associated with the effect of HRT on LDL-C oxidation (324).

HRT has a negative modulatory effect on E-selectin, VCAM-1, ICAM-1, MCP-1, and TNF- α , and an inconsistent effect on IL-6, and a stimulatory effect on TGF- β (reviewed in ref. 325). In rabbits basal and hypercholesterolemia-induced increases in MCP-1 protein are modulated by estrogens (326). Also, the anti-atherogenic effects of estrogens may be mediated by inhibition of Ang II-induced leukocyte recruitment through endothelial NO and prostacyclin release in vivo (327).

In an animal model of atherosclerosis E2 restores FasL expression, which is suppressed by atherogenic levels of serum cholesterol (328). High levels of Hcy diminish with estrogen (reviewed in ref. 329). In HUVEC, E2 caused a decrease in expression of the NADPH oxidase subunit gp91phox, up-regulated eNOS expression, and inhibited the increase in adhesion molecule and chemokine expression in cells exposed to cyclic strain. Cyclic strain enhanced endothelial O₂ formation, thereby offsetting the inhibitory effect of NO on the expression of these gene products (330).

Estrone (E1) and E2 are produced in SMC of the human aortic wall, and their production is mediated by aromatase and 17 β -hydroxysteroid dehydrogenase type I (17 β -HSD I), respectively. Also, aromatase overexpression, possibly as a result of alternative splicing, may play some role in the development of atherosclerosis (the levels of aromatase mRNA were significantly higher in female cases than in male cases and higher in the specimens with fibroatheroma than other lesions [331]). Estrone sulfate (E1S) is a major circulating plasma estrogen that is converted into the biologically active estrogen, E1, by steroid sulfatase (STS). E1 is also sulfated and reverted into E1S by estrogen sulfotransferase (EST). STS expression levels were found to be significantly higher in the VSMCs obtained from female aortas with mild atherosclerotic changes than in those with severe atherosclerotic changes, and in male aortas regardless of atherosclerotic changes. EST expression levels in the VSMCs of these aortas, however, were significantly higher in female aortas with severe atherosclerotic changes and in male aortas than in female aortas with mild atherosclerotic changes. IL-1 β markedly inhibited the expression of STS mRNA and enzyme activity, but stimulated the expression of EST mRNA and enzyme activity. In addition, IL-1 β also reduced E2 production from E1S and E1 in VSMCs (332).

Progesterone is an inhibitor of human VSMC proliferation induced by hyperglycemia and hyperinsulinemia *in vitro* (333). However, in The Heart and Estrogen/Progestin Replacement Study (HERS) carotid B-mode ultrasound examinations substudy, there were no significant treatment effects on carotid IMT (334). Also, in the Los Angeles Atherosclerosis Study the common carotid artery IMT was significantly related to years since bilateral oophorectomy, even though 90% of this group had a history of HRT. This finding which conflicts with a concept that such therapy reverses the adverse effect of bilateral oophorectomy on CHD (335). HRT significantly increased antibodies against Hsp 65 and against LDL with a low degree of oxidative modification. The hormone-mediated immune response may trigger an inflammatory response within the vessel wall and potentially increase plaque burden (336). Also, oral

contraceptives increase the risk of developing CAD in users with CVD risk factors (reviewed in ref. 337). In addition, estradiol promotes osteoblastic differentiation and calcification on vascular cells (arterial calcification increases the risk of MI) (338).

Men have higher androgen receptors than women in macrophages and dihydrotestosterone causes an increase in macrophage CE content in men but not in women (339). Also, men have enhanced oxidative stress compared to women (340).

However, in ARIC higher total testosterone (T) and sex hormone-binding globulin (SHBG) were found to be inversely related to carotid atherosclerosis in postmenopausal women not using HRT (341). In elderly males, total T levels were inversely independently associated with anti-oxLDL antibodies (342); and, hypotestosteronemia may accelerate the development of atherosclerosis and increase the risk for CHD in obese men in a cross-sectional study (343), T appears to suppress activation of pro-inflammatory cytokines, and men with low T levels are at increased risk of CAD (reviewed in ref. 344).

Dehydroepiandrosterone sulfate (DHEA-S) is inversely associated with cardiovascular death in males but not females. DHEA-S correlated positively with HDL-C and negatively with LDL-C, and the mean atherogenic index in a cross-sectional study in men and women (345). An early cardiovascular involvement was detected in severely obese normotensive premenopausal women with hyperinsulinaemia and low DHEA-S, even in the absence of other well-known CVD risk factors (346).

LIPOPROTEINS

Low-Density Lipoprotein

LDL-C is known to cause numerous cellular changes that contribute to the atherosclerotic process through the subendothelial retention of Apo B 100 containing lipoproteins, followed by biologic responses to the retained material (reviewed in ref. 347). One of the first alterations in EC function induced by LDL-C is an attenuation of endothelial-dependent vasodilation. This reduced responsiveness to vasodilation occurs before any clinical evidence of atherosclerosis. Studies in isolated vessels from normal animals demonstrate a reduction in endothelial-dependent vasodilation within minutes of exposure to oxLDL (348,349).

Lipoprotein Uptake

Lipid homeostasis is dependent on the interaction between receptor mediated and enzymatic reactions that regulate cholesterol and triglycerides. Receptor mediated lipoprotein uptake occurs through different mechanisms:

1. Macrophages express LDL receptors that recognize Apo B- and Apo E-containing lipoproteins. LDL receptors are down regulated by intracellular cholesterol (350). In mice, macrophage LDL receptor is partly responsible for lipid accumulation in foam cells when VLDL is increased under dietary stress, but not with extreme LDL accumulation (351).
2. Scavenger receptors (SR) (reviewed in ref. 352) recognize modified lipoproteins such as acetylated LDL, oxLDL, or malondialdehyde LDL as well as other negatively charged substances in a nonregulated way (350,353,354). This results in a massive lipid accumulation. Deletion of the SR class A in inbred mouse strain macrophage has no impact on plasma lipids, but causes a reduction in atherosclerotic lesion areas (355), whereas SR class A overexpression in Kupffer cells of the liver of Apo E deficient mice may scavenge atherogenic particles more efficiently from the blood compartment, and thus may cause decreased VLDL-C levels and thus have a protective effect (356).
3. Fc receptor, under certain conditions, can mediate the uptake of lipoprotein-antibody complexes, which results in lipid accumulation (350).
4. The receptor for AGE mediates uptake of glycated lipoprotein (RAGE) (354).
5. Scavenger receptor for phosphatidylserine and oxidized lipoproteins (SR-PSOX) in humans may be involved in oxLDL uptake, and subsequent foam cell transformation in macrophages in vivo (357).
6. Apo B48, a new receptor which binds and internalizes TG-rich lipoproteins, was identified in human M/M. It is colocalized in human atherosclerotic lesion foam cells (358).

Mice with double KO (dKO) to LDLr related protein 5 and Apo E have severe hypercholesterolemia, and advanced atherosclerosis compared to Apo E KO mice (359). LDLr related protein-1 mediates suppression of SMC migration induced by PDGF, and prevents atherosclerosis by controlling PDGF receptor activation by forming a complex with PDGF receptor (360).

Nonreceptor mediated uptake of lipoprotein by macrophages can also occur by phagocytosis or through secretory enzymes released by macrophages (350). The most important of these enzymes is lipoprotein lipase (LPL), which hydrolyzes TG to FFA. FFAs can be taken up by macrophages and re-esterified. This results in a marked increase in TG accumulation (361,362). In inbred mouse strains, susceptibility to atherosclerosis is associated with high macrophage LPL secretion and mRNA levels (363). In transgenic mice, smooth muscle-derived LPL translocates to the endothelium; increased LPL-mediated FFA loading initiates vascular dysfunction via PKC-mediated activation of endothelial NADPH oxidase despite normal lipoprotein levels (364). However,

LPL in post-heparin plasma is unrelated to the presence or extent of CAD (365), and transgenic rabbits overexpressing LPL are protected against diet-induced hypercholesterolemia and atherosclerosis (366).

In addition to LPL, macrophages secrete oxygen-free radicals, proteases, and Apo E, all of which affect lipoprotein accumulation (350,353). In the ARIC study, Apo E epsilon 2/3 was associated with carotid atherosclerosis, probably through delayed clearance of TG-rich lipoproteins (367). Apo E-deficient mice develop hyperlipidemia and atherosclerosis, and the lipoprotein oxidation occurs in macrophage-rich areas in early lesions. However, in necrotic areas of advanced lesions oxidation occurs diffusely in the extracellular areas (368). Physiologic levels of Apo E in the vessel wall are antiatherogenic in conditions of severe hyperlipidemia, and can affect later stages of plaque development (369).

The enhancement of receptor-mediated-TG-rich lipoprotein uptake is multifactorial. Two very important factors include *conformational changes* in apoproteins resulting in increased affinity for LDL receptor (362), and *loss of Apo C* (361). Apo C1 acts by interfering with Apo E-mediated lipoprotein uptake, but Apo C1 also has actions independent of Apo E (370).

Sphingomyelin (SM) correlate with the severity of CAD; SMase yields ceramide, ceramide levels are increased in atherosclerotic plaques and in LDL isolated from these lesions. LDL showed SMase activity that could be involved in nonreceptor-mediated endocytotic entry of LDL into cells. Also, LDL aggregation seems to involve ceramide because ceramide has a tendency for self-aggregation (reviewed in ref. 371). Ceramide produces oxidative stress in human EC, thereby reducing bioactive NO (372).

Lipoprotein Modification

Lipoprotein modification takes place in VSMC, EC, and macrophages. One such modification consists of *peroxidation* of PUFA in LDL, a process that can be inhibited by vitamin E (373). In another cross-sectional study, circulating oxLDL was associated with carotid and femoral artery IMT and plaque occurrence and with TNF- α and CRP (374).

15-Lipoxygenase is important in early human atherosclerosis, whereas in advanced lesions the enzyme is silent and its products, that were accumulated earlier, may be decomposed or superimposed by large amounts of nonenzymatic lipid peroxidation products (375). There is an important *in vivo* role of vascular 12/15 lipoxygenase in VSMC growth, migration, and matrix responses associated with atherosclerosis (376).

Advanced atheromas (in eroded or ruptured plaques) contain myeloperoxidase (MPO), which produces the pro-oxidant species hypochlorous acid (HOCl). Granulocyte macrophage colony-stimulating factor (GM-CSF), but not macrophage colony-stimulating factor (M-CSF), regulates the ability of macrophages to express MPO. Also, pro-inflammatory stimuli, such as CD40 ligand, LysoPC, or cholesterol crystals induce release of MPO (377). The generation of tyrosyl radicals by MPO allows activated phagocytes to damage both proteins and lipids (reviewed in ref. 378). However, MPO deficient LDL-receptor deficient mice on a high-fat, high-cholesterol diet had larger atherosclerotic lesions, so MPO was protective in these mice (379).

It is hypothesized that superoxide produced by neutrophils causes further lipid peroxidation of native LDL and produces oxLDL, which is the source of ceroid pigment in human foam cells (380). There is a vicious cycle of increased NADPH oxidase-dependent superoxide anion formation, augmented generation and uptake of oxLDL, and further potentiation of oxidative stress by oxLDL itself, AII, and ET-1 in EC (reviewed in ref. 381). ET-1 stimulated uptake of oxLDL in HUVEC and induces lectin-like oxLDL receptor-1 (LOX-1) via ET-1 receptor B. ET-1 receptor blockade reduces the formation of atherosclerotic lesions in experimental studies (382). Mildly oxidized LDL induces NADPH oxidase expression and superoxide anion formation in HUVEC (383). p47phox(-/-) SMCs had diminished superoxide production and a decreased proliferative response to growth factors compared with wild-type cells supporting the hypothesis that superoxide generation in general, and NADPH oxidase in particular, have a requisite role in atherosclerotic lesion formation (384).

In WHHL rabbits, aortic accumulation of hydroxide of CE and TG is not required nor is α -tocopherol depleted during atherosclerosis (385). It was suggested that the atherogenicity of oxLDL in cultured human aortic SMC is a result of LDL aggregation and not oxidation (386). PC hydroxyalkenals, a class of oxidized PC, are present in vivo and possess multiple functions characteristic of oxLDL and 4-hydroxynonenal (387).

Copper-zinc superoxide dismutase (CuZn-SOD) inhibits cell-mediated oxidation of LDL, but transgenic mice overexpressing CuZn-SOD might have increased atherosclerotic lesion area (388). The role of copper in atherosclerosis is difficult to predict and the studies are conflicting: copper is an intrinsic constituent of SOD and ceruloplasmin and a component of Lysyl oxidase (the enzyme involved in collagen synthesis, a major component of ECM). Also, copper ions catalyze oxidative modification of LDL in vitro and possibly in vivo (reviewed in ref. 389).

Enzymatically modified LDL (E-LDL): combined treatment with trypsin, cholesterol esterase, and neuraminidase transforms LDL, but not HDL or VLDL to particles with properties akin to those of lipid extracted from atherosclerotic lesions. Triple enzyme treatment disrupts the ordered and uniform structure of LDL particles, and gives rise to the formation of inhomogeneous lipid droplets 10–200 nm in diameter with a pronounced net negative charge, but lacking significant amounts of oxidized lipid (390).

LDL modification by group X secretory phospholipase A2 (sPLA2-X) in the arterial vessels is one of the mechanisms responsible for the generation of atherogenic lipoprotein particles. sPLA2-X was found to induce potent hydrolysis of PC in LDL leading to the production of large amounts of unsaturated FA and lyso-PC, which contrasted with little, if any, lipolytic modification of LDL by the classic types of group IB and IIA secretory PLA2s. Treatment with sPLA2-X caused an increase in the negative charge of LDL with little modification of Apo B in contrast to the excessive aggregation and fragmentation of Apo B in oxLDL (391).

The Influences of Modified Lipoproteins

The oxidized fatty acid fragments and sterols diffuse out of LDL into adjacent cells to exert chemotaxis, and the trapping of monocytes into the atherosclerotic lesion as macrophages. oxLDL also alters gene expression for and secretion of growth factors and cytokines by macrophages and EC (115).

Influences on Endothelial Cells

1. oxLDL activation of LOX-1 (the receptor for oxLDL identified on EC) causes activation of NF κ B through increased ROS in EC, followed by induction of adhesion molecules and endothelial apoptosis. LOX-1 expression is induced in vitro by many inflammatory cytokines, oxidative stress, hemodynamic stimuli, and oxLDL. In vivo, the expression is induced by hypertension, hyperlipidemia, and diabetes, and is accumulated in the atherosclerotic lesions. Besides oxLDL, LOX-1 can recognize apoptotic/aged cells, activated platelets, and bacteria (reviewed in ref. 392).
2. Incubation with oxLDL enhances EC production of colony stimulating factors (115). However, MCSF prevents atherosclerosis progression in WHHL rabbits by increasing net CE hydrolysis (393).
3. oxLDL is a chemo-attractant to monocytes, induces monocyte-binding protein, and stimulates the production of MCP-I by EC (115). Oxidized membrane vesicles and apoptotic blebs stimulate EC to specifically bind monocytes, with oxidized phospholipids being the active principle

and responsible for biological activity in MVs and apoptotic blebs (394). LDL, IDL, chylomicrons, and postprandial remnant particles, but not VLDL when mildly oxidized by fibroblasts overexpressing 15-lipoxygenase, increased monocyte chemotaxis and adhesion to EC, although chylomicron and VLDL had an increased 18:1/18:2 ratio (and should be less susceptible to oxidation). Only chylomicrons had no PAF-acyl hydrolase (PAF-AH). Similarly, Japanese subjects with decreased PAF-AH activity stimulated adhesion more. This activity resided in the lipid fraction and could be blocked by PAF receptor antagonist; so the above activity is related to 18:1/18:2 ratio and PAF-AH activity, and that phospholipids such as PAF are generated during lipoprotein oxidation (395). In addition, in Japanese patients with vascular occlusive disease a missense mutation G994T in PAF-AH was significantly more frequent than in controls. Patients with the mutation had more risk factors of CAD and stroke than controls with normal genotypes. Also, within the normal genotype subgroups plasma PAF-AH activity was higher in patients with vascular occlusive disease than in controls (396). In HAEC, phospholipid peroxidation generate free saturated and unsaturated aldehydes and esterified aldehydes (core aldehydes) (aldose reductase may be involved in preventing inflammation and diminishing oxidative stress early in atherosclerosis due to its ability to reduce lipid- derived aldehydes) (397). The binding of CE core aldehydes to LDL might represent the process common to the oxidative modification of lipoprotein (398).

Influences on Thrombogenicity

Vascular thrombogenicity is induced by progressive LDL oxidation, and alterations of the antioxidant/oxidant balance of LDL particle in favor of the antioxidant tone are protective against the thrombotic response triggered by oxidative stress (399). oxLDL may promote expression of CD40 and CD40L in human atheromas. Platelet-enriched plasma of mice deficient in CD40L showed markedly delayed fibrin clot formation (400). oxLDL induces surface tissue factor pathway and dysregulates fibrinolysis with a net increase in the inhibitory rate (reviewed in ref. 401).

Effects of Diabetes on LDL Oxidation

Diseases that enhance LDL oxidation include diabetes and hypertriglyceridemia (115). Hyperglycemia increases LDL oxidation, in part, through an increase in glycation products, which subsequently enhances free radical production in stimulated inflammatory cells (115). Insulin and IGF-I cause an upregulation of LDL receptor and down regulation of HDL receptor (281). Insulin increases uptake and esterification of

LDL-C by VSMC (3). LDL from diabetic patients is more atherogenic and more likely to be bound (by affinity chromatography on *Ricinus communis* agglutinin-agarose). Bound LDL has lower sialic acid content and higher fructosyl lysine level, and induces cholesterol accumulation in cultured cells and has lower neutral lipids. Desialylated LDL has a low neutral carbohydrate level, decreased content of major lipids, small size, high density, increased electronegative charge, less phospholipids, and unesterified cholesterol on their surface, with resultant altered tertiary Apo B structure with more exposure of proteoglycans-binding regions and high affinity binding of small dense LDL to arterial proteoglycans. Secretory phospholipase A2 (PLA2) in arterial tissue or plasma reduces phospholipid content in the surface monolayer LDL leading to the formation of small, dense LDL with an enhanced tendency to interact with proteoglycans. The circulating level of secretory phospholipase A2-IIA is an independent risk factor for CAD. Transgenic mice expressing human group IIA secretory phospholipid A2 spontaneously develop atherosclerotic lesions with lower HDL-C and higher LDL/VLDL-C. Also, group IIAs PLA2 can contribute to atherosclerotic lesion development through a mechanism independent of systemic lipoprotein metabolism (402). However, in mice, endogenous mouse secretory phospholipase AII gene does not significantly affect HDL or atherosclerosis (403; reviewed in ref. 404). Incubation of LDL with serum induces desialylation, through enzymes close to sialyltransferase, leading to the above changes in addition to loss of α -tocopherol from LDL, increased LDL susceptibility to oxidation, and accumulation of cholesterol covalently bound to Apo B, a marker of lipoperoxidation. Therefore, in diabetics LDL is smaller, denser, electronegative, desialylated, and glycated (405–407; and reviewed in ref. 408). However, a different study concluded that asialylated LDL has little value as a risk factor for coronary atherosclerosis in CAD patients (409). Large numbers of small Apo B 100-containing lipoproteins are far more atherogenic than lower numbers of large Apo B 100-containing lipoproteins despite nearly identical cholesterol levels (reviewed in ref. 410). Thus, both hyperinsulinemia and increased oxidation of LDL-C likely contribute to the accelerated atherosclerosis of diabetes mellitus.

The role of Apo B containing lipoproteins other than LDL has been reviewed in ref. 411. β VLDL enhances iNOS expression and nitrite accumulation in IL-1 β -stimulated VSMC (412). In rat aortic SMC, remnant lipoproteins transactivate EGF receptor via PKC and the shedding of membrane-bound soluble heparin-binding EGF-like growth factor from SMCs, resulting in SMC proliferation (413).

Oxidative Stress

Oxidative stress includes, in addition to LDL oxidation, the cellular production of ROS. Protein thiol groups are important targets for post-translational protein modification by ROS (reviewed in ref. 414), and advanced oxidation protein products were found to be an independent risk factor for CAD (415). ROS function through several mechanisms including xanthine oxidase, NAD(P)H oxidases, and NOS. Also, oscillatory shear is a potent stimulus of superoxide production (reviewed in ref. 416). Oxidative stress in humans with CAD is exacerbated by a reduction of vascular extracellular SOD (reviewed in ref. 417).

8-isoprostane (8-epiPGF[2 α]) is a marker of antioxidant deficiency and oxidative stress status in vivo. High plasma levels of 8-epiPGF(2 α) are associated with the extent and severity of CAD, and with the occurrence of different atherosclerotic risk factors (418). However, the elevated levels of another biomarker of oxidative stress, thiobarbituric acid reaction substances (TBARS), were associated with increased risk of CVD prevalence, but not after adjusting for glucose (419).

Oxidative DNA damage and repair increase significantly in human atherosclerotic plaque (420). In human aortic VSMC, oxidative stress increases ET-1 generation and autocrine ET-1 activity in VSMC, contributing to endothelial dysfunction (421). α 1 antitrypsin (AT) is produced and oxidized by macrophages, then attached to LDL in the intimal layer of the arterial wall. Although oxidized AT-LDL complex that escapes into the blood stream can be cleared by hepatocytes, the remaining can be taken up by macrophages and contribute to lipid accumulation in arterial wall cells as the early stage of atherosclerosis (422).

There is increased reactive carbonyl compound (RCO) with attendant protein modification (carbonyl stress) in atherosclerosis carbonyl stress might be derived from hyperglycemia (and lipedemia), oxidative stress, and/or impaired detoxification of RCO (423).

Antioxidant Defenses

1. Thioredoxin, a thiol-disulfide oxidoreductase, is possibly involved in antioxidant protection in human coronary arteries (424).
2. Exercise-induced plasma oxidative stress could be responsible for the prevention of atherosclerosis by stimulating arterial antioxidant response. In addition, vitamin E could be deleterious in exercisers by inhibiting antioxidant enzyme buildup in the arterial wall in LDL receptor $-/-$ male mice fed an atherogenic diet (425).
3. In humans, a greater activity of antioxidant enzyme in intracranial arteries may contribute to their greater resistance to atherosclerosis.

With increasing age intracranial arteries respond with accelerated atherogenesis when their antioxidant protection decreases, relatively more than that of extracranial arteries (426).

4. Uncoupling protein 2 (UCP2) regulates the production of ROS in macrophages, and it has a protective role against atherosclerosis (427).
5. The p66(Shc^{-/-}) mouse is the unique genetic model of increased resistance to oxidative stress and prolonged life span in mammals (428).

Other Harmful Factors

Phospholipid transfer protein (PLTP) (carrier protein that shuttles between lipoproteins to redistribute lipids) deficiency in mice is associated with decreased atherosclerosis despite decreased HDL levels. Two mechanisms are involved: decreased Apo B-containing lipoprotein production and levels, and increased antioxidation potential. Human studies indicated that PLTP activity positively correlated with aging, obesity, DM, and CAD (reviewed in ref. 429). PLTP mRNA protein expression and activity was increased by cholesterol loading of macrophages. PLTP increased HDL binding to biglycan, suggesting a role in lipoprotein retention on ECM (430).

Acyl CoA:cholesterol acyltransferase (ACAT) in Apo E/LDLr double KO mice, may be responsible for lipid accumulation in atherosclerotic lesions, and its inhibition diminishes the lipid deposition via a direct effect on macrophages in the arterial wall (431). In atherosclerotic plaque, the ability of macrophage foam cell transformation may be augmented by the dual expressions of ACAT1 and ACAT2 (432). ACAT2 deficiency, in Apo E deficient mice, results in decreased CE synthesis in the small intestine and the liver. ACAT2-derived CE has a crucial role in the development of atherosclerosis in mice and suggest that TG-rich Apo B-containing lipoproteins are not as atherogenic as those containing CE (433).

Bile salt dependent lipase, also known as carboxyl ester lipase, secreted by acinar cells of the pancreas and associated with LDL in blood, locates with SMC in atherosclerotic lesions and triggers SMC proliferation (434). It may also play a role in lipoprotein metabolism and oxLDL-induced atherosclerosis (reviewed in ref. 435).

Clusterin/apolipoprotein J (Apo J), a conserved secreted glycoprotein, has been associated with normal and premature senescence. Its serum levels are increased with age and in CHD patients (436).

Other Protective Factors

Hepatic lipase (HL) is synthesized de novo by macrophages in addition to the liver (437). Low HL activity in humans is associated with

CAD, and the presence of T allele at position -514 in the HL promoter that leads to reduced promoter activity was associated with lower HL activity and higher CAD extent (438). Increased hydrolysis of CE by the overexpression of hormone sensitive lipase leads to complete elimination of CE from foam cells by increasing efflux and decreasing influx of cholesterol (439).

TGF- β 1 inhibited the activity and expression of two key components needed for VLDL-remnants uptake, LPL and LDL receptor. TGF- β 1 inhibited CE mass induced by oxVLDL-remnants in part by decreasing the expression of scavenger receptor type AI/II and CD36. Furthermore, TGF- β 1 enhanced cholesterol efflux through upregulation of the ATP-binding cassette (ABC) transporters ABCA1 and ABCG1 (440).

Iron

In a prospective study, serum ferritin was one of the strongest risk predictors of atherosclerotic progression. The mechanism appeared to be through modification of LDL-C atherogenic potential. Lowering iron stores was beneficial during the follow-up period, also, LDL-C and ferritin were synergistic. This study could explain gender differences in atherosclerosis (441). However, there are conflicting data. In a case control study, ARIC, no association could be found between body iron stores and early atherosclerosis (442). In New Zealand White rabbits on a chow diet containing 1% (wt/wt) cholesterol, iron overload decreased atherosclerosis secondary to decreased cholesterol levels. Iron overload and deficiency had no effect on LDL oxidation susceptibility, and iron deficiency had no effect on atherosclerosis (443).

Lipoprotein(a)

The role of lipoprotein(a) [Lp(a)] in the atherosclerotic process has been extensively reviewed (444,445). Lp(a) is an LDL-like particle with Apo B100 and Apo (a) components, the latter similar to plasmin (445). A summary of the effects of Lp(a) on the atherosclerotic process is summarized in Table 3.

A cross-sectional study, ARIC, suggest that Lp(a) is a risk factor for preclinical and clinical atherosclerosis (446). However, it was found to be an independent factor associated with thickening of common carotid arteries only in severely hypercholesterolemic patients, and not in patients with moderately elevated or normal levels of blood cholesterol (447). Also, Lp(a) transgenic mice develop lipid lesions in aorta more frequently than nontransgenic animals even on a low-fat diet (448).

Table 3
Some Effects of Lp(a) on Factors in the Development of Atherosclerosis

1. Interferes with clot lysis mechanisms
 - Down regulates plasmin
 - Facilitates matrix lipoprotein deposition
 - Increases plasminogen activator inhibitor (PAI)-1
 2. Increase plaque formation
 - Facilitates macrophage migration into VSMC
 - Promotes intimal deposition of Apo B
 - Inhibits TGF- β activity
-

Normal vasculature does not contain Lp(a), however, the vascular content of Lp(a) increases in a variety of inflammatory conditions (445); large amounts of Lp(a) are found in atherosclerotic lesions. In early atherosclerotic lesions in humans and animals, there is a dramatic deposition of Lp(a) on the thickened intimal endothelial surface (445). Whereas LDL in atherosclerotic arteries is exclusively blood-derived, the accumulation of Lp(a) within the artery may be caused in part to in situ production of Apo A within the vessel wall (449).

Lp(a) can be modified by oxidative events and by the actions of lipolytic and proteolytic enzymes in the generation of products that exhibit atherothrombogenic potential (reviewed in ref. 450); oxidized Lp(a) is more potent than native Lp(a) in stimulating human VSMC growth (451). Small size Apo A isoforms may represent a cardiovascular risk factor by themselves or with plasma Lp(a) concentrations (reviewed in ref. 450).

The Effects of Lp(a)

1. Lp(a) stimulates VCAM-1 and E-selectin production by cultured human coronary artery EC (452).
2. Lp(a) in tissues may promote VSMC migration by down regulating plasmin generation at the cell surface, and thereby inhibit latent TGF- β activation (445). Thus, Lp(a) may indirectly increase VSMC migration as TGF- β normally inhibits this process (445);
3. Lysosomal acid lipase (LAL) expression is suppressed in monocytes from patients with Lp(a) hyperlipidemia and by purified Lp(a). IL-6 secretion was also induced by purified Lp(a) (453).
4. Apo (a) is produced in situ in the vessel wall. Lp(a) binds and inactivates TFPI and induces PAI type 2 expression in monocytes (reviewed in ref. 454). Apo A has antithrombotic potential as a result of its plasmino-

gen-like properties at the endothelial and subendothelial intima: (1) At the endothelial surface, high plasma levels of Lp(a) can interfere with plasminogen-plasmin conversion and clot lysis (455), and (2) Lp(a) can traverse endothelium and accumulate in intima as lipid poor Apo B100-Apo A complex or free Apo A (445). High Lp(a) plasma levels and increased endothelial permeability increases the transfer of Lp(a) to the intima (444). Once in the intima Lp(a) can complex with glycosaminoglycans, proteoglycans, or fibrin. Lp(a) can aggregate and also bind to glucosaminoglycans, fibrin, and fibronectin, and gets retained in the ECM and phagocytosed by macrophage. Plasmin enhances the binding of Lp(a) to immobilized fibrinogen and fibrin leading to increased incorporation of fibrin into the vessel wall (445).

5. Lp(a) levels are related to HLA class 2 in males with early CAD, and it is suggested that an autoimmune process may occur in patients with inherited high Lp(a) levels with certain HLA class 2 genotypes (456). Lp(a) also becomes incorporated into macrophages in the intima leading to formation of foam cells (457).

Thus, Lp(a) appears to be an important factor in promoting atherogenesis under certain conditions, however, Lp(a) has potential regenerative and antineoplastic properties that might paradoxically counterbalance its atherothrombogenicity as attested by the compatibility between raised plasma Lp(a) levels and longevity (reviewed in ref. 458).

High-Density Lipoprotein

HDL, in contrast to LDL, is thought to protect against development of atherosclerosis. The effects of HDL are summarized in Table 4. A prospective study in Japanese-American men (the Honolulu Heart Program) has shown that the risk of atherosclerosis is increased in subjects with low HDL-C and high TG when TC is borderline high or high but not when TC is desirable, independent of other risk factors (459). Increasing HDL-C levels in Apo E KO mice retards progression of advanced atherosclerotic lesions and remodels them to a more stable appearing phenotype (460).

Decreased Apo A1 appears to be a major component of the dyslipidemic serum profile in patients with atherosclerotic occlusive disease of the lower extremities (461). Despite similar TC and HDL-C levels, A1 HDL is more anti-atherogenic than A1/A2 HDL in transgenic mice (462). This is because lecithin:cholesterol acyltransferase (LCAT) and cholesteryl ester transfer protein (CETP) are present mainly in Lp A1 and because Lp A1:A2 can inhibit Lp A1-promoted cholesterol efflux. Also, mice overexpressing Apo A1 have more cholesterol efflux and are more protected against atherosclerosis mediated through decreased foam cell

Table 4
Some Effects of HDL-Cholesterol on Atherosclerotic Process

Reverse cholesterol transport*
Inhibits VSMC mitogens and matrix formation
Stimulates endothelial cell repair
Stimulates arterial endothelial cell PGI ₂ synthesis
Facilitates metabolism of triglyceride rich lipoproteins
Faciliates fibrinolysis

*Protects LDL from oxidation.

formation in vivo, and mice overexpressing Apo A2 have the opposite effects (463,464). Apo A1 expression from macrophages protects against atherosclerosis without affecting plasma Apo A1 and HDL-C levels (465).

Transgenic mice expressing CETP had worse atherosclerosis as a result of CETP-induced alterations in the lipoprotein profile (466). Also, humans with heterozygous CETP deficiency and HDL-C > 60 mg/dL have a reduced risk of CHD (reviewed in ref. 467). However, CETP inhibition alone did not have an anti atherogenic effect in a rabbit model of severe hypercholesterolemia, suggesting a relatively minor effect of raising HDL (through CETP inhibition) as compared with a decrease in non-HDL-C or TG levels (468). On the other hand, in humans CETP is expressed in macrophages in the atherosclerotic lesions and may possess an antiatherogenic function to remove cholesterol from the cells (469).

LCAT deficiency in LDLr^{-/-} mice and Apo E^{-/-} mice fed an atherogenic diet, resulted in aortic cholesterol deposition likely caused by a reduction in plasma HDL, increased saturation of CE in apo B lipoproteins, and in the Apo E^{-/-} background, increased plasma Apo B lipoprotein concentration (470). LCAT-deficient mice are associated with an increase in oxidative stress that is paradoxically reversed in a hyperlipidemic background possibly caused by the redistribution of paraoxonase (PON) to the non-HDL fraction. This may in part contribute to the reduced atherosclerosis seen in Apo E^{-/-} xLCAT^{-/-} mice (this could explain the surprising finding that LCAT-deficient subjects have severe hypoalphalipoproteinemia yet are not prone to premature CHD) (471).

Apo AII alters reverse cholesterol transport, but also may inhibit LCAT activity (deleterious effect), CETP activity (beneficial effect), may increase hepatic lipase activity (beneficial effect), and may inhibit the hepatic cholesteryl uptake from HDL (deleterious effect) (reviewed in ref. 472). There is a positive association of Apo AII with FFA and

VLDL-TG plasma concentration. Apo AII transgenic mice have increased concentration of Apo B-containing lipoproteins and increased atherosclerotic susceptibility. They also have impairment of two functions: reverse cholesterol transport and protection of LDL oxidative modification (reviewed in ref. 473).

ATP-binding cassette transporter class A1 (ABCA1) transmembrane protein is crucial for efficient efflux of cellular cholesterol and HDL maturation. Mutations in ABCA1 are the cause of Tangier disease characterized by near absent HDL (reviewed in ref. 474). ABCA1 might regulate intestinal cholesterol absorption. Unsaturated FA can reduce ABCA1 gene activity by enhancing its degradation, where liver X receptors (LXR) agonists significantly increase expression of ABCA1 gene. Preliminary evidence suggests that increasing ABCA1 gene expression may be beneficial in the prevention of diet-induced atherosclerosis (reviewed in ref. 475). Early in free cholesterol (FC) loading of macrophages, there is an increased degradation of ABCA1 with consequent decreased ABCA1-mediated cholesterol and phospholipid efflux. Also, in advanced atherosclerosis foam cells accumulate FC contributing to foam cell death and lesional necrosis (476).

Individuals with ABCA1 mutations had lower amounts of cholesterol efflux, lower HDL-C, and greater IMT than controls (477). Apo E $-/-$ mice overexpressing human ABCA1 developed smaller less complex lesions, had increased efflux of cholesterol from macrophages, their HDL particles were significantly better acceptor of cholesterol, and had increased phospholipid levels, which correlated significantly with their ability to enhance cholesterol efflux (478). Additionally, in LDLr $-$ and Apo E $-/-$ mice complete absence of ABCA1 has a major impact on plasma lipoprotein homeostasis, and the proposed anti-atherogenic effect resulting from ABCA1 deficiency is compensated by a less atherogenic profile. However, in ABCA1 deficiency in macrophages only the anti-atherogenic properties of ABCA1 are demonstrable independent of plasma lipids and HDL levels (479).

Scavenger receptor class B type 1 (SR B1) facilitates the efflux of cholesterol in peripheral tissues to HDL and mediates the selective uptake of CE from HDL in the liver. SR B1 deficiency in mice is associated with deregulation of cholesterol homeostasis in the arterial wall, resulting in increased susceptibility to atherosclerosis with increased expression of inflammatory markers and lipid deposition in the aorta (480). Inflammatory mediators down regulate SR B1 in macrophages (481).

HDL, obtained from monkeys, is susceptible to oxidation and oxidized HDL caused a decrease in free cholesterol efflux, an increase in

LDL uptake by macrophages, a decrease in monocyte antioxidant enzymes, and an increase in the number of monocytes adherent to endothelium (482). PON is an esterase associated with HDL that destroys oxidized lipids by hydrolyzing LDL-associated phospholipids and CE hydroperoxides. Low CHD risk is associated with polymorphism of PON-1 (reviewed in ref. 483). PON-1 activity and concentration were significantly lower in subjects with CHD than in control subjects (484). In inbred mice on atherogenic diet that are either susceptible or resistant to atherosclerosis, loss of HDL ability to protect against LDL oxidation is associated with decreased serum PON levels, and, in recombinant inbred mice derived from the parental strains, low PON mRNA levels segregated with aortic lesion development (485). In addition, a pro-atherosclerotic diet reduced PON activity in transgenic rabbits overexpressing Apo A1. However, the areas covered by lesions were similar to the control group (486). Human PON-1 transgenic mice (dietary or Apo E null mouse models) had significantly reduced atherosclerotic lesions, and HDL isolated from these mice protected against LDL oxidation (487). Also, PON-11 inhibits macrophage cholesterol biosynthesis and atherogenesis in mice (488). In mice, increased macrophage PON-2 expression under oxidative stress could represent a selective cellular response to reduce oxidative burden that may lead to attenuation of macrophage foam cell formation (489). Other factors that protect LDL against oxidation, and thus shown to attenuate progression or prevent the atherosclerotic process include antioxidants such as vitamins C and E and the trace element magnesium (490,491). These antioxidants may have a particularly important prophylactic role in diabetic patients who are especially prone to LDL oxidation.

Premature atherosclerosis can occur in patients with familial chylomicronemia resulting from mutation in the LPL gene (492). Approximately 1 in 20 male patients with atherosclerosis have a Asn291Ser mutation in the human LPL gene that is associated with decreased LPL activity and HDL levels (the relative frequency of this mutation is higher in patients with lower HDL levels) (493).

sPLA(2)-X (involved in the pathogenesis of atherosclerosis via potent lipolysis of LDL leading to macrophage foam cell formation) as well as group V secretory PLA(2) (sPLA(2)-V) [another group of sPLA(2) that can potently hydrolyze phosphatidylcholine (PC)] also possess potent hydrolytic potency for PC in HDL linked to the production of a large amount of unsaturated fatty acids and LysoPC. Modification with sPLA(2)-X or -V resulted in significant decrease in the capacity of HDL to cause cellular cholesterol efflux from lipid-loaded macrophages (494).

Endothelial lipase is synthesized and functions at the endothelium, and has primarily phospholipase A1 and TG lipase activities. No endothelial lipase activity was detected under basal condition, however, its expression is highly regulated by cytokines and physical forces. It is a major determinant of HDL concentration, structure, and metabolism in mice and a major determinant of HDL concentration in humans: its expression in animals leads to decreased HDL-C levels, so it might play a role in atherosclerosis development (reviewed in refs. 495–497).

Diet-induced reduction in plasma HDL shows a physiological and a genetic correlation with repression of cholesterol-7- α -hydroxylase, the liver specific enzyme that regulates the conversion of cholesterol into bile acids. Constitutively expressing this enzyme in mice prevented them from developing atherosclerosis and developing decreased HDL-C levels (498).

Effects of HDLs

HDL inhibits monocyte chemotaxis, inhibits the adhesion of monocyte and blood cell to vascular endothelium, inhibits endothelial dysfunction and apoptosis, inhibits LDL oxidation, inhibits complement activation, reduces platelet aggregability and coagulation, inhibits platelet activation, and inhibits factor X activation. HDL helps maintain endothelial integrity, facilitate vascular relaxation, stimulates the proliferation of EC and SMC, stimulates the synthesis of prostacyclin and natriuretic peptide C in EC, stimulates protein C and S activation, and may favor fibrinolysis. These functions are exerted by different components of HDL, this complexity emphasizes that changes in HDL functioning rather than plasma HDL-C levels determine the anti-atherogenicity of therapeutic alterations of HDL metabolism (reviewed in refs. 499 and 500).

Other Factors Involved in HDL Metabolism

LXR are nuclear receptors activated by oxysterols. Their activation may protect against tissue cholesterol overload (reviewed in ref. 501). LXR and their ligands are negative regulators of macrophage inflammatory gene expression, in addition to being established mediators of lipid-inducible gene expression (reviewed in ref. 502). The elimination of macrophage LXR activity causes aberrant regulation of cholesterol transporter expression, lipid accumulation in macrophages, splenomegaly, and increased atherosclerosis, suggesting that LXRs are endogenous inhibitors of atherogenesis (503). Similar results were found in mice depleted for LXR α and β with impaired TG metabolism, increased LDL-C, and decreased HDL-C (504). Additionally, LXR activation induces the expression of PLTP in the liver and in macrophages. PLTP is highly expressed in macrophages within human atherosclerotic lesions

(505). Also, LXR α and LXR β inhibit basal and cytokine-inducible expression of MMP-9 in murine peritoneal macrophages (506).

PPARs enhance cholesterol efflux and stimulate critical steps of the reverse cholesterol transport pathway (reviewed in ref. 507). PUFA and activating PPAR increase hepatic cholesterol uptake. PPAR γ induces expression of SR B1 in rat hepatocytes, liver EC, and Kupffer cells (508). PPAR α activation in human macrophages and foam cells results in an enhanced availability of free cholesterol for efflux through the ABCA1 pathway by reducing cholesterol esterification rates and ACAT1 activity (509).

PPAR γ may have an anti-atherosclerotic action by inhibiting thromboxane receptor gene expression in VSMC (510). PDGF-induced PPAR γ expression in human aortic VSMC; this PDGF-induced PPAR expression might provide a feedback mechanism by which PPAR γ inhibits PDGF-induced VSMC proliferation and migration (511).

However, PPAR α and γ increase human macrophage LPL secretion (vascular wall LPL is proatherogenic) (512). Also, PPAR Δ controls the inflammatory status of the macrophage; deletion of PPAR Δ from foam cells increased the availability of inflammatory suppressors, which in turn reduced atherosclerotic lesion area by more than 50% (513).

Fatty-acid binding proteins (FABP) are involved in fatty acid metabolism and cellular lipid transport. Adipocyte FABP (aP2) is also expressed in macrophages; bone marrow transplantation from Apo E $-/-$, aP2 $-/-$ mice to Apo E $-/-$ mice led to the development of smaller atherosclerotic lesions in recipient mice without differences in cholesterol, glucose, or insulin in plasma (514).

oxLDL-mediated increases in aP2 gene expression accelerate CE accumulation, which is important in converting macrophages to foam cells. aP2 is detected in foam cells in active atherosclerotic lesions. The induction of aP2 expression by oxLDL involves activation of PPAR γ by components of oxLDL that also function as PPAR γ ligands suggesting that PPAR γ agonists, i.e., TZD, might exacerbate atherosclerosis (515).

EXTRACELLULAR MATRIX

Production of ECM is regulated by a number of growth factors:

1. In Apo E deficient mice there is an important role for leukocyte-derived osteopontin (OPN) in mediating AII-accelerated atherosclerosis and aneurysm formation (516).
2. Human vessels susceptible to atherosclerosis showed increased accumulation of subendothelial proteoglycans (caused by increased synthesis and not to decreased degradation) mediated by TGF- β (517).

Several ECM components have an influence on the atherosclerotic process. OPN is a soluble secreted phosphoprotein that binds with high affinity to several integrins, and it has been found at the site of atherosclerotic lesions. In OPN transgenic mice, the expression of OPN induces medial thickening without injury and neointimal formation after injury (518). OPN is atherogenic and macrophages expressing OPN can be easily activated and thus promote atheromatous lesions if a high fat diet is consumed in mice (519).

Other ECM components include connexin43 (Cx43) (520), caveolin (Cav)-1 (521), collagen VIII (522), lumican protein (523), and galactosaminoglycans (524).

ECM–Lipoproteins Interaction

Regions of blood vessels that accumulate proteoglycans have a high propensity to accumulate lipid, particularly in areas associated with endothelial regrowth (72). LDL-proteoglycan complexes have been isolated from different regions of ECM within atherosclerotic vessels.

Lipids influence the proteoglycan content of the vascular wall and proteoglycans, and, consequently, influence lipid deposition in VSMC and macrophages (72). Proteoglycans accomplish this by altering the charge of lipids, decreasing degradation of LDL, and increasing CE synthesis by macrophages (72). Endothelial-derived proteoglycans bind to and modify LDL so that it becomes more negatively charged, allowing greater recognition by macrophages and incorporation to form foam cells. ECM proteoglycans bind and retain specific positively charged domains on Apo B and Apo E lipoproteins with resultant modifications altering their interaction with ECM molecules (525). The interaction between atherogenic lipoproteins and proteoglycans involves an ionic interaction between basic amino acids in Apo B 100 and negatively charged sulphate groups on the proteoglycans. Mice expressing proteoglycan binding-defective LDL developed significantly less atherosclerosis than mice expressing wild type control LDL, therefore, subendothelial retention of Apo B100-containing lipoproteins is an early step in atherosclerosis (526). The interaction of ECM with Apo B100 lipoproteins causes structural modification in lipoproteins that increase their susceptibility to proteases, phospholipases, and free radical-mediated processes (527).

oxLDL, growth factors, and cytokines influence proteoglycan structure, rendering them more likely to bind and retain lipoproteins (525). In vitro, elevated levels of nonesterified fatty acids (NEFA) alters the matrix of EC basement membrane, making them more permeable to macromolecules. NEFA causes changes in the expression of genes controlling

the proteoglycan composition from human arterial SMC, causing formation of a matrix with high affinity for LDL (reviewed in ref. 527).

Extracellular Matrix Degradation

Vascular remodeling, defined as any enduring change in the size and/or composition of an adult blood vessel, allows adaptation and repair. On the other hand, inappropriate remodeling, including its absence, underlies the pathogenesis of major cardiovascular diseases such as atherosclerosis and restenosis. Because degradation of ECM scaffold enables reshaping of tissue, participation of specialized enzymes called MMPs has become the object of intense recent interest in relation to physiological (*good*) and pathological (*bad*) vascular remodeling. The major drivers of vascular remodeling, hemodynamics, injury, inflammation, and oxidative stress regulate MMP expression and activity. Alternatively, nonspecific MMP inhibition seems to oppose remodeling as suggested by the inhibition of intimal thickening and outward arterial remodeling. MMP-related genetic variation may contribute to heterogeneity in the presentation and natural history of atherosclerosis (reviewed in ref. 528). In vitro evidence suggests that MMP activity may facilitate atherosclerosis, plaque destabilization, and platelet aggregation (reviewed in ref. 529).

Degradation of ECM can influence plaque rupture. MMPs were implicated in this process through imbalance with endogenous inhibitors. Tissue factor pathway inhibitor (TFPI)-2 is one such inhibitor whose expression, in contrast to the classic tissue inhibitor of MMPs (TIMPs), correlated negatively with MMP level in human atheromas. TFPI-2 colocalized with SMC in the normal media and fibrous cap, but weakly at the site of plaque rupture (macrophage enriched shoulder region). Human phagocytes, an abundant source of MMP, lost their ability to express this inhibitor during their differentiation in vitro (530).

Lipoproteins can influence matrix-degrading enzymes, thus influencing plaque stability (525). LDL increases the secretion of MMP-1 and collagen 1 mRNA in cultured human skin fibroblasts, thus LDL affects tissue remodeling (531). However, Apo E KO mice expressing MMP-1 specifically in the macrophage and on atherogenic diet, demonstrated decreased lesion size without plaque rupture (lesions were less extensive and immature with fewer cellular layers, and diminished contents of fibrillar collagen) (532).

MMP-9 appears to be involved, not only in degradation, but also in reorganization of a collagenous matrix, both facets being essential for the outcome of arterial remodeling (533). Serum MMP-9 is elevated in patients with severe coronary stenosis compared with controls (arterial inflammation is reflected in increased serum concentration of MMP-9)

(534). Leukocyte-derived MMP-9 is associated with aortic wall degeneration and aneurysm formation (535).

Increased expression of several cathepsins in atherosclerotic lesions suggests that these proteases may participate in the remodeling of ECM associated with the atherosclerotic process (536). Human atherosclerotic lesions overexpress cathepsin S (lysosomal cysteine protease) and have low levels of the endogenous cathepsin S inhibitor, cystatin C, compared with normal arteries. LDL receptor $-/-$ cathepsin S $-/-$ mice developed less atherosclerosis than LDL receptor $-/-$ mice (537).

Plasmin, generated by macrophage-secreted u-PA, activates pro-MMP-3 produced by accumulated macrophages. MMP-3 activity may then contribute to a reduction of plaque size, possibly by degradation of matrix components, and promote aneurysm formation by degradation of the elastica lamina (538).

COX-2 and prostaglandin E synthase (PGES) are colocalized in symptomatic lesions. Synthesis of COX-2 and PGES by activated macrophages is associated with acute ischemic syndromes, possibly through MMP-induced plaque rupture (539).

The Role of Extracellular Matrix in Vascular Calcification and Ossification

Proteoglycans accumulate in intimal lesions of large and small vessels in atherosclerosis, and may enhance the calcification associated with increasing complexity of the atherosclerotic lesion. In bovine aortic media, arterial calcification can be regulated by matrix composition (increased in the presence of collagen 1 and fibronectin and decreased in the presence of collagen IV) through interaction with $\alpha 5$ integrins (540).

Bone formation tends to occur in heavily calcified carotid lesions devoid of ulceration and hemorrhage; patients with extensive calcification of the carotid plaques are less likely to have symptomatic disease (541). When human atherosclerotic plaques demonstrated calcification or bone formation, bone morphogenetic protein (BMP)-2, BMP-4, osteopontin, and osteonectin were upregulated. Interestingly, this upregulation was associated with a sustained immunoreactivity of matrix Gla protein, osteocalcin, and bone sialoprotein (542). Osteoprotegerin (OPG) serum levels are associated with the severity of CAD and are increased in elderly men and patients with diabetes mellitus, thus increased OPG serum levels may reflect advanced cardiovascular disease in men (543). Endochondral ossification is another possible mechanism by which calcification of vascular tissue may occur in oophorectomized aged female Sprague Dawley rats (544).

Lp(a) accelerates advanced atherosclerotic lesion formation and may play an important role in vascular calcification through increased alkaline phosphatase activity and enhanced calcium accumulation in cultured rabbit aortic SMC (545).

HDL reduces osteoblastic differentiation and calcification of vascular cells. HDL also inhibited the osteogenic activity that was induced by IL-1 β , IL-6, and oxLDL. Oxidation of HDL renders it pro-osteogenic (546).

Macrophage TNF- α and oncostatin M, only when applied together, increased alkaline phosphatase activities and in vitro calcification in human VSMC in the presence of IFN- γ and 1 α ,25-dihydroxyvitamin D3 (547). Thus, proteoglycans and other extracellular substances contribute significantly to the progression of the atherosclerotic lesion.

PHYSIOLOGICAL ANTAGONISTS OF ATHEROSCLEROSIS

Macrophages synthesize and release growth factors, cytokines, adhesive glycoproteins, prostaglandins, and leukotrienes. One of the prostaglandins PGI2 has significant antiatherosclerotic properties. PGI2 synthesis is reduced in human, rabbit, and rat atherosclerotic blood vessels (72). DM reduces PGI2 synthesis in rats, an effect that is additive in the presence of an increased blood cholesterol (11). Other factors that decrease vascular eicosanoid synthesis include smoking, aging, and viral infections. This might be related, in part, to decreased arachidonic acid availability for synthesis of PGI2 (72). These eicosanoids, particularly PGI2 and PGE2, normally hydrolyze cellular CE forming free cholesterol, which is more readily removed from the cell (72). HDL induces PGI2 production in vascular EC and VSMC, which contributes to HDL-mediated cholesterol efflux (72). Also, endogenous PGE2 may modulate inflammation during atherogenesis (548).

Cholesterol enriched VSMC (foam cells) synthesize less eicosanoid, and thus are not as responsive to the cholesterol efflux effects of HDL. EC synthesize PGI2 in response to thrombin, bradykinin, leukotrienes, kallikreins, immune complexes, complement complexes, histamine, serotonin, and AII (72). Thus, EC themselves can modulate the production of factors that impact on the atherosclerotic process.

REFERENCES

1. Basha BJ, Sowers JR. Atherosclerosis: an update. *Am Heart J* 1996; 131: 1192–1202.
2. Soufi M, Sattler AM, Maisch B, Schaefer JR. Molecular mechanisms involved in atherosclerosis. *Herz* 2002; 27:637–648.
3. Fox CS, Polak JF, Chazaro I, et al. Framingham Heart Study. Genetic and environmental contributions to atherosclerosis phenotypes in men and women: heritabil-

- ity of carotid intima-media thickness in the Framingham Heart Study. *Stroke* 2003; 34:397–401.
4. Loktionov A. Common gene polymorphisms and nutrition: emerging links with pathogenesis of multifactorial chronic diseases. *J Nutr Biochem* 2003; 14:426–451.
 5. Szitanyi P, Janda J, Poledne R. Intrauterine undernutrition and programming as a new risk of cardiovascular disease in later life. *Physiol Res* 2003; 52:389–395.
 6. Napoli C, Glass CK, Witztum JL, et al. Influence of maternal hypercholesterolemia during pregnancy on progression of early atherosclerotic lesions in childhood: Fate of Early Lesions in Children (FELIC) study. *Lancet* 1999; 354:1234–1241.
 7. Washino K, Takada H, Nagashima M, Iwata H. Significance of the atherosclerogenic index and body fat in children as markers for future, potential coronary heart disease. *Pediatr Int* 1999; 41:260–265.
 8. McGill HC Jr, McMahan CA, Herderick EE, et al. Origin of atherosclerosis in childhood and adolescence. *Am J Clin Nutr* 2000; 72:1307S–1315S.
 9. Kunz J. Initial lesions of vascular aging disease (arteriosclerosis). *Gerontology* 2000; 46:295–299.
 10. Su TC, Jeng JS, Chien KL, et al. Hypertension status is the major determinant of carotid atherosclerosis: a community-based study in Taiwan. *Stroke* 2001; 32:2265–2271.
 11. McFarlane SI, Banerji M, and Sowers JR: Insulin resistance and cardiovascular disease. *J Clin Endocrinol Metab* 2001; 86:713–718.
 12. Jensen JS, Borch-Johnsen K, Jensen G, Feldt-Rasmussen B. Atherosclerotic risk factors are increased in clinically healthy subjects with microalbuminuria. *Atherosclerosis* 1995; 112:245–252.
 13. Management of type 2 diabetes: long-awaited evidence of benefits after blood sugar control. *Prescrire Int* 1999; 8:147–152.
 14. Segura J, Campo C, Ruilope LM. Proteinuria. An underappreciated risk factor in cardiovascular disease. *Curr Cardiol Rep* 2002; 4:458–462.
 15. Diercks GF, Stroes ES, van Boven AJ, et al. Urinary albumin excretion is related to cardiovascular risk indicators, not to flow-mediated vasodilation, in apparently healthy subjects. *Atherosclerosis* 2002; 163:121–126.
 16. Jiang Y, Kohara K, Hiwada K. Low wall shear stress contributes to atherosclerosis of the carotid artery in hypertensive patients. *Hypertens Res* 1999; 22:203–207.
 17. Stehbens WE. Relevance of hypercholesterolemia to fetal and pediatric atherosclerosis. *Pediatr Pathol Mol Med* 2002; 21:259–578.
 18. Noris M, Morigi M, Donadelli R, et al. Nitric oxide synthesis by cultured endothelial cells is modulated by flow conditions. *Circ Res* 1995; 76:536–543.
 19. Yoshisue H, Suzuki K, Kawabata A, et al. Large scale isolation of non-uniform shear stress-responsive genes from cultured human endothelial cells through the preparation of a subtracted cDNA library. *Atherosclerosis* 2002; 162:323–334.
 20. Jin X, Iwasa S, Okada K, et al. Shear stress-induced collagen XII expression is associated with atherogenesis. *Biochem Biophys Res Commun* 2003; 308:152–158.
 21. Chen XL, Varner SE, Rao AS, et al. Laminar flow induction of antioxidant response element-mediated genes in endothelial cells. A novel anti-inflammatory mechanism. *J Biol Chem* 2003; 278:703–711.
 22. Paszkowiak JJ, Dardik A. Arterial wall shear stress: observations from the bench to the bedside. *Vasc Endovascular Surg* 2003; 37:47–57.
 23. Silacci P, Desgeorges A, Mazzolai L, Chambaz C, Hayoz D. Flow pulsatility is a critical determinant of oxidative stress in endothelial cells. *Hypertension* 2001; 38:1162–1166.

24. Okano M, Yoshida Y. Junction complexes of endothelial cells in atherosclerosis-prone and atherosclerosis-resistant regions on flow dividers of brachiocephalic bifurcations in the rabbit aorta. *Biorheology* 1994; 31:155–161.
25. Eriksson EE, Xie X, Werr J, Thoren P, Lindbom L. Importance of primary capture and L-selectin-dependent secondary capture in leukocyte accumulation in inflammation and atherosclerosis in vivo. *J Exp Med* 2001; 194:205–218.
26. Prasad A, Koh KK, Schenke WH, et al. Role of angiotensin II type 1 receptor in the regulation of cellular adhesion molecules in atherosclerosis. *Am Heart J* 2001; 142:248–253.
27. Mazzolai L, Silacci P, Bouzourene K, et al. Tissue factor activity is upregulated in human endothelial cells exposed to oscillatory shear stress. *Thromb Haemost* 2002; 87:1062–1068.
28. Khrenov AV, Ananyeva NM, Griffin JH, Saenko EL. Coagulation pathways in atherothrombosis. *Trends Cardiovasc Med* 2002; 12:317–324.
29. Ananyeva NM, Kouivaskaia DV, Shima M, Saenko EL. Intrinsic pathway of blood coagulation contributes to thrombogenicity of atherosclerotic plaque. *Blood* 2002; 99:4475–4485.
30. Kato H. Regulation of functions of vascular wall cells by tissue factor pathway inhibitor: basic and clinical aspects. *Arterioscler Thromb Vasc Biol* 2002; 22:539–548.
31. Makin AJ, Chung NA, Silverman SH, Lip GY. Vascular endothelial growth factor and tissue factor in patients with established peripheral artery disease: a link between angiogenesis and thrombogenesis? *Clin Sci* 2003; 104:397–404.
32. Huber K, Christ G, Wojta J, Gulba D. Plasminogen activator inhibitor type-1 in cardiovascular disease. Status report 2001. *Thromb Res* 2001;103:S7–S19.
33. Luttun A, Lupu F, Storkebaum E, et al. Lack of plasminogen activator inhibitor-1 promotes growth and abnormal matrix remodeling of advanced atherosclerotic plaques in apolipoprotein E-deficient mice. *Arterioscler Thromb Vasc Biol* 2002; 22:499–505.
34. Ishii H, Yoshida M, Hiraoka M, et al. Recombinant annexin II modulates impaired fibrinolytic activity in vitro and in rat carotid artery. *Circ Res* 2001; 89:1240–1245.
35. Falkenberg M, Tom C, DeYoung MB, et al. Increased expression of urokinase during atherosclerotic lesion development causes arterial constriction and lumen loss, and accelerates lesion growth. *Proc Natl Acad Sci USA* 2002; 99:10,665–10,670.
36. Auld GC, Ritchie H, Robbie LA, Booth NA. Thrombin upregulates tissue transglutaminase in endothelial cells: a potential role for tissue transglutaminase in stability of atherosclerotic plaque. *Arterioscler Thromb Vasc Biol* 2001; 21:1689–1694.
37. Levenson J, Giral P, Razavian M, Garipey J, Simon A. Fibrinogen and silent atherosclerosis in subjects with cardiovascular risk factors. *Arterioscler Thromb Vasc Biol* 1995; 15:1263–1268.
38. Koenig W, Rothenbacher D, Hoffmeister A, Griesshammer M, Brenner H. Plasma fibrin D-dimer levels and risk of stable coronary artery disease: results of a large case-control study. *Arterioscler Thromb Vasc Biol* 2001; 21:1701–1705.
39. Rezaee F, Gijbels MJ, Offerman EH, et al. Overexpression of fibrinogen in ApoE*3-Leiden transgenic mice does not influence the progression of diet-induced atherosclerosis. *Thromb Haemost* 2002; 88:329–334.
40. Lovely RS, Falls LA, Al-Mondhiry HA, et al. Association of gammaA/gamma' fibrinogen levels and coronary artery disease. *Thromb Haemost* 2002; 88:26–31.
41. Huang M, Pang X, Letourneau R, Boucher W, Theoharides TC. Acute stress induces cardiac mast cell activation and histamine release, effects that are increased in Apolipoprotein E knockout mice. *Cardiovasc Res* 2002; 55:150–160.

42. Leskinen MJ, Kovanen PT, Lindstedt KA. Regulation of smooth muscle cell growth, function and death in vitro by activated mast cells—a potential mechanism for the weakening and rupture of atherosclerotic plaques. *Biochem Pharmacol* 2003; 66:1493–1498.
43. Lee M, Calabresi L, Chiesa G, Franceschini G, Kovanen PT. Mast cell chymase degrades apoE and apoA-II in apoA-I-knockout mouse plasma and reduces its ability to promote cellular cholesterol efflux. *Arterioscler Thromb Vasc Biol* 2002; 22:1475–1481.
44. Dell'Italia LJ, Husain A. Dissecting the role of chymase in angiotensin II formation and heart and blood vessel diseases. *Curr Opin Cardiol* 2002; 17:374–379.
45. Tsao PS, Theilmeyer G, Singer AH, Leung LL, Cooke JP. L-arginine attenuates platelet reactivity in hypercholesterolemic rabbits. *Arterioscler Thromb* 1994; 14:1529–1533.
46. Cassar K, Bachoo P, Ford I, Greaves M, Brittenden J. Platelet activation is increased in peripheral arterial disease. *J Vasc Surg* 2003; 38:99–103.
47. Theilmeyer G, Michiels C, Spaepen E, et al. Endothelial von Willebrand factor recruits platelets to atherosclerosis-prone sites in response to hypercholesterolemia. *Blood* 2002; 99:4486–4493.
48. Sachais BS, Kuo A, Nassar T, et al. Platelet factor 4 binds to low-density lipoprotein receptors and disrupts the endocytic machinery, resulting in retention of low-density lipoprotein on the cell surface. *Blood* 2002; 99:3613–3622.
49. Nassar T, Sachais BS, Akkawi S, et al. Platelet factor 4 enhances the binding of oxidized low-density lipoprotein to vascular wall cells. *J Biol Chem* 2003; 278:6187–6193.
50. Gawaz M, Neumann FJ, Dickfeld T, et al. Activated platelets induce monocyte chemotactic protein-1 secretion and surface expression of intercellular adhesion molecule-1 on endothelial cells. *Circulation* 1998; 98:1164–1171.
51. Huo Y, Schober A, Forlow SB, et al. Circulating activated platelets exacerbate atherosclerosis in mice deficient in apolipoprotein E. *Nat Med* 2003; 9:61–67.
52. Di Virgilio F, Solini A. P2 receptors: new potential players in atherosclerosis. *Br J Pharmacol* 2002; 135:831–842.
53. Moulton KS, Vakili K, Zurakowski D, et al. Inhibition of plaque neovascularization reduces macrophage accumulation and progression of advanced atherosclerosis. *Proc Natl Acad Sci USA* 2003; 100:4736–4741.
54. Bonetti PO, Lerman LO, Lerman A. Endothelial dysfunction: a marker of atherosclerotic risk. *Arterioscler Thromb Vasc Biol* 2003; 23:168–175.
55. Poredos P. Endothelial dysfunction in the pathogenesis of atherosclerosis. *Int Angiol* 2002; 21:109–116.
56. Blann AD, Seigneur M, Steiner M, Boisseau MR, McCollum CN. Circulating endothelial cell markers in peripheral vascular disease: relationship to the location and extent of atherosclerotic disease. *Eur J Clin Invest* 1997; 27:916–921.
57. Cooke JP. Does ADMA cause endothelial dysfunction? *Arterioscler Thromb Vasc Biol* 2000; 20:2032–2037.
58. Albrecht EW, Stegeman CA, Heeringa P, Henning RH, van Goor H. Protective role of endothelial nitric oxide synthase. *J Pathol* 2003; 199:8–17.
59. Isenovic ER, Divald A, Milivojevic N, et al. Interactive effects of insulin-like growth factor-1 and beta-estradiol on endothelial nitric oxide synthase activity in rat aortic endothelial cells. *Metabolism* 2003; 52:482–487.
60. Gonzalez-Santiago L, Lopez-Ongil S, Rodriguez-Puyol M, Rodriguez-Puyol D. Decreased nitric oxide synthesis in human endothelial cells cultured on type I collagen. *Circ Res* 2002; 90:539–545.

61. Ozaki M, Kawashima S, Yamashita T, et al. Overexpression of endothelial nitric oxide synthase accelerates atherosclerotic lesion formation in apoE-deficient mice. *J Clin Invest* 2002; 110:331–340.
62. Ma J, Nakajima T, Iida H, et al. Inhibitory effects of ursodeoxycholic acid on the induction of nitric oxide synthase in vascular smooth muscle cells. *Eur J Pharmacol* 2003; 464:79–86.
63. Isenovic ER, Meng Y, Divald A, Milivojevic N, Sowers JR. Role of phosphatidylinositol 3-kinase/Akt pathway in angiotensin II and insulin-like growth factor-1 modulation of nitric oxide synthase in vascular smooth muscle cells. *Endocrine* 2002; 19:287–292.
64. Morishita T, Tsutsui M, Shimokawa H, et al. Vasculoprotective roles of neuronal nitric oxide synthase. *FASEB J* 2002; 16:1994–1996.
65. Boger RH. The emerging role of asymmetric dimethylarginine as a novel cardiovascular risk factor. *Cardiovasc Res* 2003; 59:824–833.
66. Chen J, Kuhlencordt P, Urano F, et al. Effects of chronic treatment with L-arginine on atherosclerosis in apoE knockout and apoE/inducible NO synthase double-knockout mice. *Arterioscler Thromb Vasc Biol* 2003; 23:97–103.
67. Mizia-Stec K, Zahorska-Markiewicz B, Mandecki T, et al. Serum levels of selected adhesion molecules in patients with coronary artery disease. *Int J Cardiol* 2002; 83:143–150.
68. Chen CH, Henry PD. Atherosclerosis as a microvascular disease: impaired angiogenesis mediated by suppressed basic fibroblast growth factor expression. *Proc Assoc Am Physicians* 1997; 109:351–361.
69. Blann AD, Belgore FM, McCollum CN, et al. Vascular endothelial growth factor and its receptor, Flt-1, in the plasma of patients with coronary or peripheral atherosclerosis, or Type II diabetes. *Clin Sci* 2002; 102:187–194.
70. Ruef J, Hu ZY, Yin LY, et al. Induction of vascular endothelial growth factor in balloon-injured baboon arteries. A novel role for reactive oxygen species in atherosclerosis. *Circ Res* 1997; 81:24–33.
71. Celletti FL, Waugh JM, Amabile PG, et al. Vascular endothelial growth factor enhances atherosclerotic plaque progression. *Nat Med* 2001; 7:425–429.
72. Cooke JP. Endothelium derived factors and peripheral vascular disease. *Cardiovascular Clinic* 1992; 22:3–17.
73. Guretzki HJ, Gerbitz KD, Olgemoller B, Schleicher E. Atherogenic levels of low density lipoprotein alter the permeability and composition of the endothelial barrier. *Atherosclerosis* 1994; 107:15–24.
74. Choy JC, Granville DJ, Hunt DW, McManus BM. Endothelial cell apoptosis: biochemical characteristics and potential implications for atherosclerosis. *J Mol Cell Cardiol* 2001; 33:1673–1690.
75. Minamino T, Miyauchi H, Yoshida T, et al. Endothelial cell senescence in human atherosclerosis: role of telomere in endothelial dysfunction. *Circulation* 2002; 105:1541–1544.
76. Le Couteur DG, Fraser R, Cogger VC, McLean AJ. Hepatic pseudocapillarisation and atherosclerosis in ageing. *Lancet* 2002; 359:1612–1615.
77. Sowers JR, Draznin B. Insulin, cation metabolism and insulin resistance. *J Basic Clin Physiol Pharmacol* 1998; 9:223–233.
78. Baltali M, Korkmaz ME, Kiziltan HT, et al. Association between postprandial hyperinsulinemia and coronary artery disease among non-diabetic women: a case control study. *Int J Cardiol* 2003; 88:215–221.
79. Iida KT, Shimano H, Kawakami Y, et al. Insulin up-regulates tumor necrosis factor-alpha production in macrophages through an extracellular-regulated kinase-dependent pathway. *J Biol Chem* 2001; 276:32,531–32,537.

80. Rask-Madsen C, Dominguez H, Ihlemann N, et al. Tumor necrosis factor- α inhibits insulin's stimulating effect on glucose uptake and endothelium-dependent vasodilation in humans. *Circulation* 2003; 108:1815–1821.
81. Okamoto Y, Kihara S, Ouchi N, et al. Adiponectin reduces atherosclerosis in apolipoprotein E-deficient mice. *Circulation* 2002; 106:2767–2770.
82. Sowers JR, Epstein M, Frohlich ED. Diabetes, hypertension, and cardiovascular disease: an update. *Hypertension* 2001; 37:1053–1059.
83. Djousse L, Pankow JS, Eckfeldt JH, et al. Relation between dietary linolenic acid and coronary artery disease in the National Heart, Lung, and Blood Institute Family Heart Study. *Am J Clin Nutr* 2001; 74:612–619.
84. Pomerantz KB, Hajjar DP. Eicosanoids in regulation of arterial VSMCs phenotype, proliferative capacity, and cholesterol metabolism. *Arteriosclerosis* 1989; 9:413–429.
85. Sperling RI, Robin J, Kylander KA et al. The effect of n-3 polyunsaturated fatty acids on the generation of platelet activating factor formation by human monocytes. *J Immunol* 1987; 139:4186–4191.
86. Barcelli U, Glas-Greenwalt P, Pollak VE. Enhancing effects of dietary supplementation with -3 fatty acids on plasma fibrinolysis in normal subjects *Thrombosis Res* 1985; 39:307–312.
87. JamesMJ, Gibson RA, Cleland LG. Dietary polyunsaturated fatty acids and inflammatory mediatorproduction. *Am J Clin Nutr* 2000; 71:343S–348S.
88. Fox PL, DiCorleto PE. Fish oils inhibit endothelial cell production of platelet-derived growth factor-like protein. *Science* 1988; 241:453–456.
89. Shimokawa H, Lam JY, Chesebro JH et al: Effect of dietary supplementation with cod-liver oil on endothelial dependent responses in porcine coronary arteries. *Circulation* 1987; 76:898–905.
90. HoM, Maple C, Bancroft A, McLaren M, Belch JJ. The beneficial effects of omega-3 and omega-6 essential fatty acids supplementation on red blood cell rheology. *ProstaglandinsLeukot Essent Fatty Acids* 1999; 61:13–17.
91. Meydani M. Soluble adhesion molecules: surrogate markers of cardiovascular disease? *Nutr Rev* 2003; 61:63–68.
92. Ntambi JM, Choi Y, Park Y, Peters JM, Pariza MW. Effects of conjugated linoleic acid (CLA) on immune responses, body composition and stearyl-CoA desaturase. *Can J Appl Physiol* 2002; 27:617–628.
93. Angerer P, Kothny W, Stork S, von Schacky C. Effect of dietary supplementation with omega-3 fatty acids on progression of atherosclerosis in carotid arteries. *Cardiovasc Res* 2002; 54:183–190.
94. Moreno JJ, Mitjavila MT. The degree of unsaturation of dietary fatty acids and the development of atherosclerosis. *J Nutr Biochem* 2003; 14:182–195.
95. Ramirez-Tortosa MC, Urbano G, Lopez-Jurado M, et al. Extra-virgin olive oil increases the resistance of LDL to oxidation more than refined olive oil in free-living men with peripheral vascular disease. *J Nutr* 1999; 129:2177–2183.
96. Massaro M, Carluccio MA, De Caterina R. Direct vascular antiatherogenic effects of oleic acid: a clue to the cardioprotective effects of the Mediterranean diet. *Cardiologia* 1999; 44:507–513.
97. De La Cruz JP, Villalobos MA, Carmona JA, et al. Antithrombotic potential of olive oil administration in rabbits with elevated cholesterol. *Thromb Res* 2000; 100:305–315.
98. Mortensen A, Hansen BF, Hansen JF, et al. Comparison of the effects of fish oil and olive oil on blood lipids and aortic atherosclerosis in Watanabe heritable hyperlipidaemic rabbits. *Br J Nutr* 1998; 80:565–573.

99. Merkel M, Velez-Carrasco W, Hudgins LC, Breslow JL. Compared with saturated fatty acids, dietary monounsaturated fatty acids and carbohydrates increase atherosclerosis and VLDL cholesterol levels in LDL receptor-deficient, but not apolipoprotein E-deficient, mice. *Proc Natl Acad Sci USA* 2001; 98: 13,294–13,299.
100. Bae JH, Bassenge E, Lee HJ, et al. Impact of postprandial hypertriglyceridemia on vascular responses in patients with coronary artery disease: effects of ACE inhibitors and fibrates. *Atherosclerosis* 2001; 158:165–171.
101. Han SN, Leka LS, Lichtenstein AH, et al. Effect of hydrogenated and saturated, relative to polyunsaturated, fat on immune and inflammatory responses of adults with moderate hypercholesterolemia. *J Lipid Res* 2002; 43:445–452.
102. Cohn JS. Oxidized fat in the diet, postprandial lipaemia and cardiovascular disease. *Curr Opin Lipidol* 2002; 13:19–24.
103. Toborek M, Hennig B. The role of linoleic acid in endothelial cell gene expression. Relationship to atherosclerosis. *Subcell Biochem* 1998; 30:415–436.
104. Bayindir O, Ozmen D, Mutaf I, et al. Comparison of the effects of dietary saturated, mono-, and n-6 polyunsaturated fatty acids on blood lipid profile, oxidant stress, prostanoid synthesis and aortic histology in rabbits. *Ann Nutr Metab* 2002; 46: 222–228.
105. van Jaarsveld PJ, Smuts CM, Benade AS. Effect of palm olein oil in a moderate-fat diet on plasma lipoprotein profile and aortic atherosclerosis in non-human primates. *Asia Pac J Clin Nutr* 2002; 11:S424–S432.
106. Gale CR, Ashurst HE, Powers HJ, Martyn CN. Antioxidant vitamin status and carotid atherosclerosis in the elderly. *Am J Clin Nutr* 2001; 74:402–408.
107. Dumesnil JG, Turgeon J, Tremblay A, et al. Effect of a low-glycaemic index—low-fat—high protein diet on the atherogenic metabolic risk profile of abdominally obese men. *Br J Nutr* 2001; 86:557–568.
108. Willcox JK, Catignani GL, Lazarus S. Tomatoes and cardiovascular health. *Crit Rev Food Sci Nutr* 2003; 43:1–18.
109. Rao AV. Lycopene, tomatoes, and the prevention of coronary heart disease. *Exp Biol Med* 2002; 227:908–913.
110. Adams MR, Golden DL, Register TC, et al. The atheroprotective effect of dietary soy isoflavones in apolipoprotein E-/- mice requires the presence of estrogen receptor-alpha. *Arterioscler Thromb Vasc Biol* 2002; 22:1859–1864.
111. Sorisky A. Molecular links between obesity and cardiovascular disease. *Am J Ther* 2002; 9:516–521.
112. Flack JM, Sowers JR: Epidemiologic and clinical aspects of insulin resistance and hyperinsulinemia. *Am J Med* 1991; 91:11S–21S.
113. Blann AD, Bushell D, Davies A, et al. von Willebrand factor, the endothelium and obesity. *Int J Obes Relat Metab Disord* 1993; 17:723–725.
114. Tanko LB, Bagger YZ, Alexandersen P, Larsen PJ, Christiansen C. Peripheral adiposity exhibits an independent dominant antiatherogenic effect in elderly women. *Circulation* 2003; 107:1626–1631.
115. Chisolm GM, Irwin KC, Penn MS. Lipoprotein oxidation and lipoprotein induced cell injury in diabetes. *Diabetes* 1992; 41:61–66.
116. Laws A, King AC, Haskell WL, et al. Relation of fasting Plasma insulin concentration to HDL-cholesterol and triglyceride concentration in men. *Arteriosclerosis and Thrombosis* 1991; 11:1636–1642.
117. Vitelli LL, Shahar E, Heiss G, et al. Glycosylated hemoglobin level and carotid intimal-medial thickening in nondiabetic individuals. The Atherosclerosis Risk in Communities Study. *Diabetes Care* 1997; 20:1454–1458.

118. Bonora E, Mugge M. Postprandial blood glucose as a risk factor for cardiovascular disease in Type II diabetes: the epidemiological evidence. *Diabetologia* 2001; 44:2107–2114.
119. Lemieux I, Pascot A, Prud'homme D, et al. Elevated C-reactive protein: another component of the atherothrombotic profile of abdominal obesity. *Arterioscler Thromb Vasc Biol* 2001; 21:961–967.
120. Kekalainen P, Sarlund H, Farin P, et al. Femoral atherosclerosis in middle-aged subjects: association with cardiovascular risk factors and insulin resistance. *Am J Epidemiol* 1996; 144:742–748.
121. Vliementhart R, Geleijnse JM, Hofman A, et al. Alcohol consumption and risk of peripheral arterial disease: the Rotterdam study. *Am J Epidemiol* 2002; 155:332–338.
122. Kiechl S, Willeit J, Rungger G, et al. Alcohol consumption and atherosclerosis: what is the relation? Prospective results from the Bruneck Study. *Stroke* 1998; 29:900–907.
123. Kiechl S, Willeit J, Egger G, Oberhollenzer M, Aichner F. Alcohol consumption and carotid atherosclerosis: evidence of dose-dependent atherogenic and antiatherogenic effects. Results from the Bruneck Study. *Stroke* 1994;25: 1593–1598.
124. Shaish A, Pape M, Rea T, et al. Alcohol increases plasma levels of cholesterol diet-induced atherogenic lipoproteins and aortic atherosclerosis in rabbits. *Arterioscler Thromb Vasc Biol* 1997; 17:1091–1097.
125. Corder R, Douthwaite JA, Lees DM, et al. Endothelin-1 synthesis reduced by red wine. *Nature* 2001; 414:863–864.
126. Maggi-Capeyron MF, Ceballos P, Cristol JP, et al. Wine phenolic antioxidants inhibit AP-1 transcriptional activity. *J Agric Food Chem* 2001; 49:5646–5652.
127. Leikert JF, Rathel TR, Wohlfart P, et al. Red wine polyphenols enhance endothelial nitric oxide synthase expression and subsequent nitric oxide release from endothelial cells. *Circulation* 2002; 106:1614–1617.
128. Rosenkranz S, Knirel D, Dietrich H, et al. Inhibition of the PDGF receptor by red wine flavonoids provides a molecular explanation for the “French paradox”. *FASEB J* 2002; 16:1958–1960.
129. Iijima K, Yoshizumi M, Ouchi Y. Effect of red wine polyphenols on vascular smooth muscle cell function—molecular mechanism of the ‘French paradox’. *Mech Ageing Dev* 2002; 123:1033–1039.
130. Auger C, Caporiccio B, Landrault N, et al. Red wine phenolic compounds reduce plasma lipids and apolipoprotein B and prevent early aortic atherosclerosis in hypercholesterolemic golden Syrian hamsters (*Mesocricetus auratus*). *J Nutr* 2002; 132:1207–1213.
131. Tsiara S, Elisaf M, Mikhailidis DP. Influence of smoking on predictors of vascular disease. *Angiology* 2003; 54:507–530.
132. Witteman JC, Grobbee DE, Valkenburg HA, et al. Cigarette smoking and the development and progression of aortic atherosclerosis. A 9-year population-based follow-up study in women. *Circulation* 1993; 88:2156–2162.
133. Garrison RJ, Kannel WB, Feinleib MP, et al. Cigarette smoking and HDL-cholesterol: The Framingham offspring study. *Atherosclerosis* 1978; 30:17–25.
134. Valkonen M, Kuusi T. Passive smoking induces atherogenic changes in low-density lipoprotein. *Circulation* 1998; 97:2012–2016.
135. Hutchison SJ, Sudhir K, Sievers RE, et al. Effects of L-arginine on atherogenesis and endothelial dysfunction due to secondhand smoke. *Hypertension* 1999; 34:44–50.
136. Wang XL, Raveendran M, Wang J. Genetic influence on cigarette-induced cardiovascular disease. *Prog Cardiovasc Dis* 2003; 45:361–382.

137. Djousse L, Myers RH, Province MA, et al. Influence of apolipoprotein E, smoking, and alcohol intake on carotid atherosclerosis: National Heart, Lung, and Blood Institute Family Heart Study. *Stroke* 2002; 33:1357–1361.
138. Weber C, Erl W, Weber K, Weber PC. Increased adhesiveness of isolated monocytes to endothelium is prevented by vitamin C intake in smokers. *Circulation* 1996; 93:1488–1492.
139. Kiechl S, Werner P, Egger G, et al. Active and passive smoking, chronic infections, and the risk of carotid atherosclerosis: prospective results from the Bruneck Study. *Stroke* 2002; 33:2170–2176.
140. Knight-Lozano CA, Young CG, Burow DL, et al. Cigarette smoke exposure and hypercholesterolemia increase mitochondrial damage in cardiovascular tissues. *Circulation* 2002; 105:849–854.
141. Schroecksadel K, Frick B, Winkler C, et al. Hyperhomocysteinemia and immune activation. *Clin Chem Lab Med* 2003; 41:1438–1443.
142. Konukoglu D, Serin O, Ercan M, Turhan MS. Plasma homocysteine levels in obese and non-obese subjects with or without hypertension; its relationship with oxidative stress and copper. *Clin Biochem* 2003; 36:405–408.
143. Folsom AR, Nieto FJ, McGovern PG, et al. Prospective study of coronary heart disease incidence in relation to fasting total homocysteine, related genetic polymorphisms, and B vitamins: the Atherosclerosis Risk in Communities (ARIC) study. *Circulation* 1998; 98:204–210.
144. O'Grady H, Kelly C, Bouchier-Hayes D, Leahy A. Homocysteine and occlusive arterial disease. *Br J Surg* 2002; 89:838–844.
145. Hofmann MA, Lalla E, Lu Y, et al. Hyperhomocysteinemia enhances vascular inflammation and accelerates atherosclerosis in a murine model. *J Clin Invest* 2001; 107:675–683.
146. Constans J, Blann AD, Resplandy F, et al. Endothelial dysfunction during acute methionine load in hyperhomocysteinemic patients. *Atherosclerosis* 1999; 147:411–413.
147. Ungvari Z, Csiszar A, Edwards JG, et al. Increased superoxide production in coronary arteries in hyperhomocysteinemia: role of tumor necrosis factor- α , NAD(P)H oxidase, and inducible nitric oxide synthase. *Arterioscler Thromb Vasc Biol* 2003; 23:418–424.
148. Stuhlinger MC, Tsao PS, Her JH, et al. Homocysteine impairs the nitric oxide synthase pathway: role of asymmetric dimethylarginine. *Circulation* 2001; 104:2569–2575.
149. Jakubowski H, Zhang L, Bardeguet A, Aviv A. Homocysteine thiolactone and protein homocysteinylation in human endothelial cells: implications for atherosclerosis. *Circ Res* 2000; 87:45–51.
150. Sainani GS, Sainani R. Homocysteine and its role in the pathogenesis of atherosclerotic vascular disease. *J Assoc Physicians India* 2002; 50:16–23.
151. Majors A, Ehrhart LA, Pezacka EH. Homocysteine as a risk factor for vascular disease. Enhanced collagen production and accumulation by smooth muscle cells. *Arterioscler Thromb Vasc Biol* 1997; 17:2074–2081.
152. Zhou J, Moller J, Danielsen CC, et al. Dietary supplementation with methionine and homocysteine promotes early atherosclerosis but not plaque rupture in ApoE-deficient mice. *Arterioscler Thromb Vasc Biol* 2001; 21:1470–1476.
153. Li J, Zhang Y, Yao X, et al. Effect of homocysteine on the L-arginine/nitric oxide synthase/nitric oxide pathway in human platelets. *Heart Vessels* 2002; 16:46–50.
154. Bruunsgaard H, Skinhoj P, Pedersen AN, Schroll M, Pedersen BK. Ageing, tumour necrosis factor- α (TNF- α) and atherosclerosis. *Clin Exp Immunol* 2000; 121:255–260.

155. Grainger DJ, Bethell HW. High titres of serum antinuclear antibodies, mostly directed against nucleolar antigens, are associated with the presence of coronary atherosclerosis. *Ann Rheum Dis* 2002; 61:110–114.
156. Chia S, Ludlam CA, Fox KA, Newby DE. Acute systemic inflammation enhances endothelium-dependent tissue plasminogen activator release in men. *J Am Coll Cardiol* 2003; 41:333–339.
157. Elkind MS, Sciacca R, Boden-Albala B, Homma S, Di Tullio MR. Leukocyte count is associated with aortic arch plaque thickness. *Stroke* 2002; 33:2587–2592.
158. Hata H, Kuga T, Takeshita A. Adherent leukocytes to the aortic wall promotes atherosclerosis in the Watanabe heritable hyperlipidemic rabbits. *Fukuoka Igaku Zasshi* 1995; 86:437–442.
159. Burke-Gaffney A, Brooks AV, Bogle RG. Regulation of chemokine expression in atherosclerosis. *Vascul Pharmacol* 2002; 38:283–292.
160. Umehara H, Bloom ET, Okazaki T, et al. Fractalkine in Vascular Biology. From Basic Research to Clinical Disease. *Arterioscler Thromb Vasc Biol* 2004; 24:34–40.
161. Lesnik P, Haskell CA, Charo IF. Decreased atherosclerosis in CX3CR1-/- mice reveals a role for fractalkine in atherogenesis. *J Clin Invest* 2003; 111:333–340.
162. Lei ZB, Zhang Z, Jing Q, et al. Oxidized LDL upregulates CXCR2 expression in monocytes via scavenger receptors and activation of p38 mitogen-activated protein kinase. *Cardiovasc Res* 2002; 53:524–532.
163. Dong ZM, Chapman SM, Brown AA, et al. The combined role of P- and E-selectins in atherosclerosis. *J Clin Invest* 1998; 102:145–152.
164. Boring L, Gosling J, Cleary M, Charo IF. Decreased lesion formation in CCR2 -/- mice reveals a role for chemokines in the initiation of atherosclerosis. *Nature* 1998; 394:894–897.
165. Aiello RJ, Bourassa PA, Lindsey S, et al. Monocyte chemoattractant protein-1 accelerates atherosclerosis in apolipoprotein E-deficient mice. *Arterioscler Thromb Vasc Biol* 1999; 19:1518–1525.
166. Namiki M, Kawashima S, Yamashita T, et al. Local overexpression of monocyte chemoattractant protein-1 at vessel wall induces infiltration of macrophages and formation of atherosclerotic lesion: synergism with hypercholesterolemia. *Arterioscler Thromb Vasc Biol* 2002; 22:115–120.
167. Nie Q, Fan J, Haraoka S, Shimokama T, Watanabe T. Inhibition of mononuclear cell recruitment in aortic intima by treatment with anti-ICAM-1 and anti-LFA-1 monoclonal antibodies in hypercholesterolemic rats: implications of the ICAM-1 and LFA-1 pathway in atherogenesis. *Lab Invest* 1997; 77:469–482.
168. Hulthe J, Wikstrand J, Mattsson-Hulten L, Fagerberg B. Circulating ICAM-1 (intercellular cell-adhesion molecule 1) is associated with early stages of atherosclerosis development and with inflammatory cytokines in healthy 58-year-old men: the Atherosclerosis and Insulin Resistance (AIR) study. *Clin Sci* 2002; 103:123–129.
169. Schreyer SA, Peschon JJ, LeBoeuf RC. Accelerated atherosclerosis in mice lacking tumor necrosis factor receptor p55. *J Biol Chem* 1996; 271:26,174–26,178.
170. Elkind MS, Cheng J, Boden-Albala B, et al. Tumor necrosis factor receptor levels are associated with carotid atherosclerosis. *Stroke* 2002; 33:31–37.
171. Osterud B, Bjorklid E. Role of monocytes in atherogenesis. *Physiol Rev* 2003; 83:1069–1112.
172. Smith DA, Zouridakis EG, Mariani M, et al. Neopterin levels in patients with coronary artery disease are independent of Chlamydia pneumoniae seropositivity. *Am Heart J* 2003; 146:69–74.

173. Jacob SS, Shastry P, Sudhakaran PR. Influence of non-enzymatically glycosylated collagen on monocyte-macrophage differentiation. *Atherosclerosis* 2001; 159:333–341.
174. Lessner SM, Prado HL, Waller EK, Galis ZS. Atherosclerotic lesions grow through recruitment and proliferation of circulating monocytes in a murine model. *Am J Pathol* 2002; 160:2145–2155.
175. Boyle JJ, Bowyer DE, Weissberg PL, Bennett MR. Human blood-derived macrophages induce apoptosis in human plaque-derived vascular smooth muscle cells by Fas-ligand/Fas interactions. *Arterioscler Thromb Vasc Biol* 2001; 21:1402–1407.
176. Linton MF, Fazio S. Cyclooxygenase-2 and atherosclerosis. *Curr Opin Lipidol* 2002; 13:497–504.
177. Frostegard J. Autoimmunity, oxidized LDL and cardiovascular disease. *Autoimmun Rev* 2002; 1:233–237.
178. Lehr HA, Sagban TA, Ihling C, et al. Immunopathogenesis of atherosclerosis: endotoxin accelerates atherosclerosis in rabbits on hypercholesterolemic diet. *Circulation* 2001; 104:914–920.
179. Torzewski J, Oldroyd R, Lachmann P, et al. Complement-induced release of monocyte chemoattractant protein-1 from human smooth muscle cells. A possible initiating event in atherosclerotic lesion formation. *Arterioscler Thromb Vasc Biol* 1996; 16:673–677.
180. Kwon KH, Kwon HM, Hong BK, et al. Autoantibody against malondialdehyde-modified low density lipoprotein in patients with non-diabetic unstable angina: a potential role in immunologic reaction of plaque instability. *Yonsei Med J* 2002; 43:203–210.
181. Ostos MA, Recalde D, Zakin MM, Scott-Algara D. Implication of natural killer T cells in atherosclerosis development during a LPS-induced chronic inflammation. *FEBS Lett* 2002; 519:23–29.
182. Shaw PX, Goodyear CS, Chang MK, Witztum JL, Silverman GJ. The autoreactivity of anti-phosphorylcholine antibodies for atherosclerosis-associated neo-antigens and apoptotic cells. *J Immunol* 2003; 170:6151–6157.
183. McDowell A, Young IS, Wisdom GB. Autoantibodies to malondialdehyde-modified low-density lipoprotein in patients with angiographically confirmed coronary artery disease. *J Pharm Pharmacol* 2002; 54:1651–1657.
184. vShaw PX, Horkko S, Tsimikas S, et al. Human-derived anti-oxidized LDL autoantibody blocks uptake of oxidized LDL by macrophages and localizes to atherosclerotic lesions in vivo. *Arterioscler Thromb Vasc Biol* 2001; 21:1333–1339.
185. Caligiuri G, Nicoletti A, Poirier B, Hansson GK. Protective immunity against atherosclerosis carried by B cells of hypercholesterolemic mice. *J Clin Invest* 2002; 109:745–753.
186. Staub HL, Norman GL, Crowther T, et al. Antibodies to the atherosclerotic plaque components beta2-glycoprotein I and heat-shock proteins as risk factors for acute cerebral ischemia. *Arq Neuropsiquiatr* 2003; 61:757–763.
187. Matsuura E, Kobayashi K, Koike T, Shoenfeld Y. Autoantibody-mediated atherosclerosis. *Autoimmun Rev* 2002; 1:348–353.
188. Schonbeck U, Libby P. CD40 signaling and plaque instability. *Circ Res* 2001; 89:1092–1103.
189. Mach F, Schonbeck U, Sukhova GK, Atkinson E, Libby P. Reduction of atherosclerosis in mice by inhibition of CD40 signalling. *Nature* 1998; 394:200–203.
190. Tellides G, Tereb DA, Kirkiles-Smith NC, et al. Interferon-gamma elicits arteriosclerosis in the absence of leukocytes. *Nature* 2000; 403:207–211.

191. Whitman SC, Ravisankar P, Daugherty A. IFN-gamma deficiency exerts gender-specific effects on atherogenesis in apolipoprotein E-/- mice. *J Interferon Cytokine Res* 2002; 22:661–670.
192. von der Thusen JH, Kuiper J, van Berkel TJ, Biessen EA. Interleukins in atherosclerosis: molecular pathways and therapeutic potential. *Pharmacol Rev* 2003; 55:133–166.
193. Lyon CJ, Law RE, Hsueh WA. Minireview: adiposity, inflammation, and atherogenesis. *Endocrinology* 2003; 144:2195–2200.
194. Plutzky J. The potential role of peroxisome proliferator-activated receptors on inflammation in type 2 diabetes mellitus and atherosclerosis. *Am J Cardiol* 2003; 92:34J–41J.
195. Kwak BR, Myit S, Mulhaupt F, et al. PPARgamma but not PPARalpha ligands are potent repressors of major histocompatibility complex class II induction in atheroma-associated cells. *Circ Res* 2002; 90:356–362.
196. Fan J, Watanabe T. Inflammatory reactions in the pathogenesis of atherosclerosis. *J Atheroscler Thromb* 2003; 10:63–71.
197. Dentan C, Lesnik P, Chapman MJ, Ninio E. Phagocytic activation induces formation of platelet-activating factor in human monocyte-derived macrophages and in macrophage-derived foam cells. Relevance to the inflammatory reaction in atherogenesis. *Eur J Biochem* 1996; 236:48–55.
198. Stannard AK, Riddell DR, Sacre SM, et al. Cell-derived apolipoprotein E (ApoE) particles inhibit vascular cell adhesion molecule-1 (VCAM-1) expression in human endothelial cells. *J Biol Chem* 2001; 276:46,011–46,016.
199. Camici M. C-reactive protein, atherosclerosis and cardiovascular disease. An update. *Minerva Cardioangiol* 2002; 50:327–331.
200. Calabro P, Willerson JT, Yeh ET. Inflammatory cytokines stimulated C-reactive protein production by human coronary artery smooth muscle cells. *Circulation* 2003; 108:1930–1932.
201. Verma S, Li SH, Badiwala MV, et al. Endothelin antagonism and interleukin-6 inhibition attenuate the proatherogenic effects of C-reactive protein. *Circulation* 2002; 105:1890–1896.
202. Devaraj S, Xu DY, Jialal I. C-reactive protein increases plasminogen activator inhibitor-1 expression and activity in human aortic endothelial cells: implications for the metabolic syndrome and atherothrombosis. *Circulation* 2003; 107:398–404.
203. Fu T, Borensztajn J. Macrophage uptake of low-density lipoprotein bound to aggregated C-reactive protein: possible mechanism of foam-cell formation in atherosclerotic lesions. *Biochem J* 2002; 366:195–201.
204. Veselka J, Prochazkova S, Duchonova R, et al. Relationship of C-reactive protein to presence and severity of coronary atherosclerosis in patients with stable angina pectoris or a pathological exercise test. *Coron Artery Dis* 2002; 13:151–154.
205. Valen G, Yan ZQ, Hansson GK. Nuclear factor kappa-B and the heart. *J Am Coll Cardiol* 2001; 38:307–314.
206. Kanters E, Pasparakis M, Gijbels MJ, et al. Inhibition of NF-kappaB activation in macrophages increases atherosclerosis in LDL receptor-deficient mice. *J Clin Invest* 2003; 112:1176–1185.
207. Ihling C, Szombathy T, Bohrmann B, et al. Coexpression of endothelin-converting enzyme-1 and endothelin-1 in different stages of human atherosclerosis. *Circulation* 2001; 104:864–869.
208. Haug C, Schmid-Kotsas A, Zorn U, et al. Endothelin-1 synthesis and endothelin B receptor expression in human coronary artery smooth muscle cells and mono-

- cyte-derived macrophages is up-regulated by low density lipoproteins. *J Mol Cell Cardiol* 2001; 33:1701–1712.
209. Bobryshev YV. Dendritic cells and their involvement in atherosclerosis. *Curr Opin Lipidol* 2000; 11:511–517.
 210. Alderman CJ, Bunyard PR, Chain BM, et al. Effects of oxidised low density lipoprotein on dendritic cells: a possible immunoregulatory component of the atherogenic micro-environment? *Cardiovasc Res* 2002; 55:806–819.
 211. Bobryshev YV, Lord RS. Expression of heat shock protein-70 by dendritic cells in the arterial intima and its potential significance in atherogenesis. *J Vasc Surg* 2002; 35:368–375.
 212. Knoflach M, Mayerl B, Mayerl C, Sedivy R, Wick G. Atherosclerosis as a paradigmatic disease of the elderly: role of the immune system. *Immunol Allergy Clin North Am* 2003; 23:117–132.
 213. Lamb DJ, El-Sankary W, Ferns GA. Molecular mimicry in atherosclerosis: a role for heat shock proteins in immunisation. *Atherosclerosis* 2003; 167:177–185.
 214. Binder CJ, Horkko S, Dewan A, et al. Pneumococcal vaccination decreases atherosclerotic lesion formation: molecular mimicry between *Streptococcus pneumoniae* and oxidized LDL. *Nat Med* 2003; 9:736–743.
 215. Xu Q. Role of heat shock proteins in atherosclerosis. *Arterioscler Thromb Vasc Biol* 2002; 22:1547–1559.
 216. Vink A, Schoneveld AH, van der Meer JJ, et al. In vivo evidence for a role of toll-like receptor 4 in the development of intimal lesions. *Circulation* 2002; 106:1985–1990.
 217. Laman JD, Schoneveld AH, Moll FL, van Meurs M, Pasterkamp G. Significance of peptidoglycan, a proinflammatory bacterial antigen in atherosclerotic arteries and its association with vulnerable plaques. *Am J Cardiol* 2002; 90:119–123.
 218. Castrillo A, Joseph SB, Vaidya SA, et al. Crosstalk between LXR and toll-like receptor signaling mediates bacterial and viral antagonism of cholesterol metabolism. *Mol Cell* 2003; 12:805–816.
 219. Bouwman JJ, Visseren FL, Bosch MC, Bouter KP, Diepersloot RJ. Procoagulant and inflammatory response of virus-infected monocytes. *Eur J Clin Invest* 2002; 32:759–766.
 220. Herzberg MC. Coagulation and thrombosis in cardiovascular disease: plausible contributions of infectious agents. *Ann Periodontol* 2001; 6:16–19.
 221. Kalayoglu MV, Libby P, Byrne GI. Chlamydia pneumoniae as an emerging risk factor in cardiovascular disease. *JAMA* 2002; 288:2724–2731.
 222. Espinola-Klein C, Rupprecht HJ, Blankenberg S, et al. AtheroGene Investigators. Impact of infectious burden on extent and long-term prognosis of atherosclerosis. *Circulation* 2002; 105:15–21.
 223. Prasad A, Zhu J, Halcox JP, et al. Predisposition to atherosclerosis by infections: role of endothelial dysfunction. *Circulation* 2002; 106:184–190.
 224. Ross R. The pathogenesis of atherosclerosis: a perspective for the 1990s. *Nature* 1993; 362: 801–809.
 225. Ross R. The pathogenesis of atherosclerosis. In: Braunwald E, ed. *Heart Disease: A Textbook of Cardiovascular Medicine*. 4th ed. Philadelphia, PA: WB Saunders Co. 1991; 2:1106–1124.
 226. Gordon D, Schwartz SM. Replication of arterial smooth muscle cells in hypertension and atherosclerosis. *Am J Cardiol* 1987; 59:44A–48A.
 227. Sims FH, Chen X, Gavin JB. The importance of a substantial elastic lamina subadjacent to the endothelium in limiting the progression of atherosclerotic changes. *Histopathology* 1993; 23:307–317.

228. Stary HC. Lipid and macrophage accumulations in arteries of children and the development of atherosclerosis. *Am J Clin Nutr* 2000; 72:1297S–1306S.
229. Ridker PM, Rifai N, Clearfield M, et al. Air Force/Texas Coronary Atherosclerosis Prevention Study Investigators. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. *N Engl J Med* 2001; 344:1959–1965.
230. Virmani R, Burke AP, Kolodgie FD, Farb A. Pathology of the thin-cap fibroatheroma: a type of vulnerable plaque. *J Interv Cardiol* 2003; 16:267–272.
231. Varnava AM, Mills PG, Davies MJ. Relationship between coronary artery remodeling and plaque vulnerability. *Circulation* 2002; 105:939–943.
232. Heidland UE, Strauer BE. Left ventricular muscle mass and elevated heart rate are associated with coronary plaque disruption. *Circulation* 2001; 104:1477–1482.
233. Herrera VM, Didishvili T, Lopez LV, et al. Hypertension exacerbates coronary artery disease in transgenic hyperlipidemic Dahl salt-sensitive hypertensive rats. *Mol Med* 2001; 7:831–844.
234. Manabe I, Nagai R. Regulation of smooth muscle phenotype. *Curr Atheroscler Rep* 2003; 5:214–222.
235. Schneider DB, Vassalli G, Wen S, et al. Expression of Fas ligand in arteries of hypercholesterolemic rabbits accelerates atherosclerotic lesion formation. *Arterioscler Thromb Vasc Biol* 2000; 20:298–308.
236. Koide M, Harayama H, Iio A, et al. Major risk factors for atherosclerosis are manifested in experimental Ca-deficiency. *Hypertens Res* 1996; 19:S35–S40.
237. Gouni-Berthold I, Sachinidis A. Does the coronary risk factor low density lipoprotein alter growth and signaling in vascular smooth muscle cells? *FASEB J* 2002; 16:1477–1487.
238. Ichikawa T, Unoki H, Sun H, et al. Lipoprotein(a) promotes smooth muscle cell proliferation and dedifferentiation in atherosclerotic lesions of human apo(a) transgenic rabbits. *Am J Pathol* 2002; 160:227–236.
239. Hayashi K, Takahashi M, Nishida W, et al. Phenotypic modulation of vascular smooth muscle cells induced by unsaturated lysophosphatidic acids. *Circ Res* 2001; 89:251–258.
240. Zhu Y, Bujo H, Yamazaki H, et al. Enhanced expression of the LDL receptor family member LR11 increases migration of smooth muscle cells in vitro. *Circulation* 2002; 105:1830–1836.
241. Nishikawa KC, Millis AJ. gp38k (CHI3L1) is a novel adhesion and migration factor for vascular cells. *Exp Cell Res* 2003; 287:79–87.
242. Ahn JD, Morishita R, Kaneda Y, et al. Inhibitory effects of novel AP-1 decoy oligodeoxynucleotides on vascular smooth muscle cell proliferation in vitro and neointimal formation in vivo. *Circ Res* 2002; 90:1325–1332.
243. Tsuda Y, Okazaki M, Uezono Y, et al. Activation of extracellular signal-regulated kinases is essential for pressure-induced proliferation of vascular smooth muscle cells. *Eur J Pharmacol* 2002; 446:15–24.
244. Andreassi MG, Botto N. DNA damage as a new emerging risk factor in atherosclerosis. *Trends Cardiovasc Med* 2003; 13:270–275.
245. Hiltunen MO, Turunen MP, Hakkinen TP, et al. DNA hypomethylation and methyltransferase expression in atherosclerotic lesions. *Vasc Med* 2002; 7:5–11.
246. Seye CI, Kong Q, Erb L, et al. Functional P2Y2 nucleotide receptors mediate uridine 5'-triphosphate-induced intimal hyperplasia in collared rabbit carotid arteries. *Circulation* 2002; 106:2720–2726.
247. Nishimoto S, Hamajima Y, Toda Y, et al. Identification of a novel smooth muscle associated protein, smap2, upregulated during neointima formation in a rat carotid endarterectomy model. *Biochim Biophys Acta* 2002; 1576:225–230.

248. Brophy CM, Woodrum DA, Pollock J, et al. cGMP-dependent protein kinase expression restores contractile function in cultured vascular smooth muscle cells. *J Vasc Res* 2002; 39:95–103.
249. Casco VH, Veinot JP, Kuroski de Bold ML, et al. Natriuretic peptide system gene expression in human coronary arteries. *J Histochem Cytochem* 2002; 50:799–809.
250. Arkenbout EK, de Waard V, van Bragt M, et al. Protective function of transcription factor TR3 orphan receptor in atherogenesis: decreased lesion formation in carotid artery ligation model in TR3 transgenic mice. *Circulation* 2002; 106:1530–1535.
251. Wada Y, Sugiyama A, Yamamoto T, et al. Lipid accumulation in smooth muscle cells under LDL loading is independent of LDL receptor pathway and enhanced by hypoxic conditions. *Arterioscler Thromb Vasc Biol* 2002; 22:1712–1719.
252. Febbraio M, Guy E, Coburn C, et al. The impact of overexpression and deficiency of fatty acid translocase (FAT)/CD36. *Mol Cell Biochem* 2002; 239:193–197.
253. Matsumoto K, Hirano K, Nozaki S, et al. Expression of macrophage (Mphi) scavenger receptor, CD36, in cultured human aortic smooth muscle cells in association with expression of peroxisome proliferator activated receptor-gamma, which regulates gain of Mphi-like phenotype in vitro, and its implication in atherogenesis. *Arterioscler Thromb Vasc Biol* 2000; 20:1027–1032.
254. Nicholson AC, Han J, Febbraio M, Silverstein RL, Hajjar DP. Role of CD36, the macrophage class B scavenger receptor, in atherosclerosis. *Ann N Y Acad Sci* 2001;947:224–228.
255. Sata M. Circulating vascular progenitor cells contribute to vascular repair, remodeling, and lesion formation. *Trends Cardiovasc Med* 2003; 13:249–253.
256. Rauscher FM, Goldschmidt-Clermont PJ, Davis BH, et al. Aging, progenitor cell exhaustion, and atherosclerosis. *Circulation* 2003; 108:457–463.
257. Goldschmidt-Clermont PJ. Loss of bone marrow-derived vascular progenitor cells leads to inflammation and atherosclerosis. *Am Heart J* 2003; 146:S5–S12.
258. Sidawy AN, Mitchell ME, Neville RF. Peptide growth factors and signal transduction. *Semin Vasc Surg* 1998; 11:149–155.
259. Keidar S, Attias J, Heinrich R, Coleman R, Aviram M. Angiotensin II atherogenicity in apolipoprotein E deficient mice is associated with increased cellular cholesterol biosynthesis. *Atherosclerosis* 1999; 146:249–257.
260. Kaplan M, Aviram M, Knopf C, Keidar S. Angiotensin II reduces macrophage cholesterol efflux: a role for the AT-1 receptor but not for the ABC1 transporter. *Biochem Biophys Res Commun* 2002; 290:1529–1534.
261. Keidar S, Heinrich R, Kaplan M, Hayek T, Aviram M. Angiotensin II administration to atherosclerotic mice increases macrophage uptake of oxidized ldl: a possible role for interleukin-6. *Arterioscler Thromb Vasc Biol* 2001; 21:1464–1469.
262. Bell L, Madri JA. Effect of platelet factors on migration of cultured bovine aortic endothelial and smooth muscle cells. *Circ Res* 1989; 65:1057–1065.
263. Harrison DG, Cai H, Landmesser U, Griendling KK. Interactions of angiotensin II with NAD(P)H oxidase, oxidant stress and cardiovascular disease. *J Renin Angiotensin Aldosterone Syst* 2003; 4:51–61.
264. Tham DM, Martin-McNulty B, Wang YX, et al. Angiotensin II is associated with activation of NF-kappaB-mediated genes and downregulation of PPARs. *Physiol Genomics* 2002; 11:21–30.
265. Tham DM, Martin-McNulty B, Wang YX, et al. Angiotensin II injures the arterial wall causing increased aortic stiffening in apolipoprotein E-deficient mice. *Am J Physiol Regul Integr Comp Physiol* 2002; 283:R1442–R1449.
266. Manning MW, Cassis LA, Daugherty A. Differential effects of doxycycline, a broad-spectrum matrix metalloproteinase inhibitor, on angiotensin II-induced atherosclerosis and abdominal aortic aneurysms. *Arterioscler Thromb Vasc Biol* 2003;23:483–488.

267. Ruiz-Ortega M, Ruperez M, Esteban V, Egido J. Molecular mechanisms of angiotensin II-induced vascular injury. *Curr Hypertens Rep* 2003; 5:73–79.
268. Nickenig G. Central role of the AT(1)-receptor in atherosclerosis. *J Hum Hypertens* 2002;16:S26–S33.
269. Sodhi CP, Kanwar YS, Sahai A. Hypoxia and high glucose upregulate AT1 receptor expression and potentiate ANG II-induced proliferation in VSM cells. *Am J Physiol Heart Circ Physiol* 2003; 284:H846–H852.
270. Daugherty A, Manning MW, Cassis LA. Antagonism of AT2 receptors augments angiotensin II-induced abdominal aortic aneurysms and atherosclerosis. *Br J Pharmacol* 2001; 134:865–870.
271. Rajagopalan S, Duquaine D, King S, Pitt B, Patel P. Mineralocorticoid receptor antagonism in experimental atherosclerosis. *Circulation* 2002; 105:2212–2216.
272. Keidar S, Hayek T, Kaplan M, et al. Effect of eplerenone, a selective aldosterone blocker, on blood pressure, serum and macrophage oxidative stress, and atherosclerosis in apolipoprotein E-deficient mice. *J Cardiovasc Pharmacol* 2003; 41:955–963.
273. Mitani H, Bandoh T, Kimura M, Totsuka T, Hayashi S. Increased activity of vascular ACE related to atherosclerotic lesions in hyperlipidemic rabbits. *Am J Physiol* 1996; 271:H1065–H1071.
274. McFarlane SI, Kumar A, Sowers JR. Mechanisms by which angiotensin-converting enzyme inhibitors prevent diabetes and cardiovascular disease. *Am J Cardiol* 2003; 91:30H–37H.
275. Yang BC, Phillips MI, Mohuczy D, et al. Increased angiotensin II type 1 receptor expression in hypercholesterolemic atherosclerosis in rabbits. *Arterioscler Thromb Vasc Biol* 1998; 18:1433–1439.
276. Bornfeldt KE, Arngvist HJ, Norstedt G. Regulation of IGF-I gene expression by growth factors in cultured vascular VSMCs. *J Endocrinol* 1990; 125:381–386.
277. Jawien A, Bowen-Pope DF, Lindner V, et al. PDGF promote smooth muscle migration and intimal thickening in a rat model of balloon angioplasty. *J Clin Invest* 1992; 89:507–511.
278. Kozaki K, Kaminski WE, Tang J, et al. Blockade of platelet-derived growth factor or its receptors transiently delays but does not prevent fibrous cap formation in ApoE null mice. *Am J Pathol* 2002; 161:1395–1407.
279. Thyberg J, Hedin U, Sjolund M, et al. Regulation of differentiated properties and proliferation of arterial VSMC. *Arteriosclerosis* 1990; 10:966–990.
280. Kanaki T, Bujo H, Mori S, et al. Functional analysis of aortic endothelial cells expressing mutant PDGF receptors with respect to expression of matrix metalloproteinase-3. *Biochem Biophys Res Commun* 2002; 294:231–237.
281. Ferns GA, Motani AS, Ånggord EE. The IGFs: Their putative role in atherogenesis. *Artery* 1991; 18:197–225.
282. Sowers JR. Insulin and insulin-like growth factor in normal and pathological cardiovascular physiology. *Hypertension* 1997; 29:691–699.
283. Sowers JR. Effects of insulin and IGF-I on vascular smooth muscle glucose and cation metabolism. *Diabetes* 1996; 45: S47–S51.
284. Che W, Lerner-Marmarosh N, Huang Q, et al. Insulin-like growth factor-1 enhances inflammatory responses in endothelial cells: role of Gab1 and MEKK3 in TNF-alpha-induced c-Jun and NF-kappaB activation and adhesion molecule expression. *Circ Res* 2002; 90:1222–1230.
285. Murphy LJ, Ghahary A, Chakrabarti S. Insulin regulation of IGF-I expression in rat aorta. *Diabetes* 1990; 39:657–662.

286. Stout RW. Insulin as a mitogenic factor: role in the pathogenesis of cardiovascular disease. *Am J Med* 1991; 90:62S–65S.
287. Rich CB, Ewton DZ, Martin BM, et al. IGF-I regulation of elastogenesis: comparison of aortic and lung cells. *Am J Physiol* 1992; 263:L276–L282.
288. Pfeifle B, Boeder H, Ditschuneit H. Interaction of receptors for insulin-like growth factor I, platelet-derived growth factor, and fibroblast growth factor in rat aortic cells. *Endocrinology* 1987; 120:2251–2258.
289. Sugimoto H, Franks DJ, Lecavalier L, Chiasson JL, Hamet P. Therapeutic modulation of growth-promoting activity in platelets from diabetics. *Diabetes* 1987; 36:667–672.
290. Geffner ME, Bersch N, Nakamoto JM, et al. Use of in vitro clonogenic assays to differentiate acquired from genetic causes of insulin resistance. *Diabetes* 1991; 40:28–36.
291. Wang R, Kudo M, Yokoyama M, Asano G. Roles of advanced glycation endproducts (AGE) and receptor for AGE on vascular smooth muscle cell growth. *J Nippon Med Sch* 2001; 68:472–481.
292. Janssen JA, Lamberts SW. The role of IGF-I in the development of cardiovascular disease in type 2 diabetes mellitus: is prevention possible? *Eur J Endocrinol* 2002; 146:467–477.
293. Juul A, Scheike T, Davidsen M, Gyllenborg J, Jorgensen T. Low serum insulin-like growth factor I is associated with increased risk of ischemic heart disease: a population-based case-control study. *Circulation* 2002; 106:939–944.
294. Zaina S, Pettersson L, Ahren B, et al. Insulin-like growth factor II plays a central role in atherosclerosis in a mouse model. *J Biol Chem* 2002; 277:4505–4511.
295. Matsumoto S, Kishida K, Shimomura I, et al. Increased plasma HB-EGF associated with obesity and coronary artery disease. *Biochem Biophys Res Commun* 2002; 292:781–786. Erratum in: *Biochem Biophys Res Commun* 2002; 295:571.
296. Bjorkerud S. Effects of TGF on human arterial VSMCs in vitro. *Arteriosclerosis and Thrombosis* 1991; 11:892–902.
297. Assoian RK, Fleurdelys BE, Stevenson HC, et al. Expression and secretion of type β TGF by activated human macrophages. *Proc Natl Acad Sci USA* 1987; 84:6020–6024.
298. Assoian RK, Komoriya A, Meyers CA, et al. Transforming growth factor- β in human platelets: identification of a major storage site, purification, and characterization. *J Biol Chem* 1983; 258:7155–7160.
299. Mallat Z, Gojova A, Marchiol-Fournigault C, et al. Inhibition of transforming growth factor-beta signaling accelerates atherosclerosis and induces an unstable plaque phenotype in mice. *Circ Res* 2001; 89:930–934.
300. Lutgens E, Gijbels M, Smook M, et al. Transforming growth factor-beta mediates balance between inflammation and fibrosis during plaque progression. *Arterioscler Thromb Vasc Biol* 2002; 22:975–982.
301. Owens GK, Geisterfer AA, Yang YW, et al. TGF-induced growth inhibition and cellular hypertrophy in cultured vascular VSMCs. *J Cell Biology* 1988; 107:771–780.
302. Ozer NK, Boscoboinik D, Azzi A. New roles of low density lipoproteins and vitamin E in the pathogenesis of atherosclerosis. *Biochem Mol Biol Int* 1995; 35:117–124.
303. Mansson PE, Malark M, Sawada H, Kan M, McKeehan WL. Heparin-binding (fibroblast) growth factors type one and two genes are co-expressed in proliferating normal human vascular endothelial and smooth muscle cells in culture. *In Vitro Cell Dev Biol* 1990; 26:209–212.

304. Bakris GL, Fairbanks R, Traish AM. Arginine vasopressin stimulates human mesangial cell production of endothelin. *J Clin Invest* 1991; 87:1158–1164.
305. Lonchamp MO, Pinelis S, Goulin J, Chabrier PE, Braquet P. Proliferation and Na⁺/H⁺ exchange activation by endothelin in vascular smooth muscle cells. *Am J Hypertens* 1991; 4:776–779.
306. Clinton SK, Libby P. Cytokines and growth factors in atherogenesis. *Arch Pathol Lab Med* 1992; 116:1292–1300.
307. Nathan CF. Secretory products of macrophages. *J Clin Invest* 1987; 79:319–326.
308. Sawada H, Kan M, McKeehan WL. Opposite effects of monokines (interleukin-1 and tumor necrosis factor) on proliferation and heparin-binding (fibroblast) growth factor binding to human aortic endothelial and smooth muscle cells. *In Vitro Cell Dev Biol* 1990; 26:213–216.
309. Anwar A, Zahid AA, Scheidegger KJ, Brink M, Delafontaine P. Tumor necrosis factor- α regulates insulin-like growth factor-1 and insulin-like growth factor binding protein-3 expression in vascular smooth muscle. *Circulation* 2002; 105:1220–1225.
310. Ikeda U, Ikeda M, Oohara T, Kano S, Yaginuma T. Mitogenic action of interleukin-1 α on vascular smooth muscle cells mediated by PDGF. *Atherosclerosis* 1990; 84:183–188.
311. Ikeda U, Ikeda M, Oohara T, et al. Interleukin 6 stimulates growth of vascular smooth muscle cells in a PDGF-dependent manner. *Am J Physiol* 1991; 260: H1713–1717.
312. Morisaki N, Koyama N, Mori S, et al. Effects of smooth muscle cell derived growth factor (SDGF) in combination with other growth factors on smooth muscle cells. *Atherosclerosis* 1989; 78:61–67.
313. Diez-Roux AV, Nieto FJ, Tyroler HA, Crum LD, Szklo M. Social inequalities and atherosclerosis. The atherosclerosis risk in communities study. *Am J Epidemiol* 1995; 141:960–972.
314. Matsumoto Y, Uyama O, Shimizu S, et al. Do anger and aggression affect carotid atherosclerosis? *Stroke* 1993; 24:983–986.
315. Kop WJ. The integration of cardiovascular behavioral medicine and psychoneuro-immunology: new developments based on converging research fields. *Brain Behav Immun* 2003; 17:233–237.
316. Kendrick M. Does insulin resistance cause atherosclerosis in the post-prandial period? *Med Hypotheses* 2003; 60:6–11.
317. Black PH, Garbutt LD. Stress, inflammation and cardiovascular disease. *J Psychosom Res* 2002; 52:1–23.
318. Spieker LE, Hurlimann D, Ruschitzka F, et al. Mental stress induces prolonged endothelial dysfunction via endothelin-A receptors. *Circulation* 2002; 105:2817–2820.
319. Kronenberg F, Pereira MA, Schmitz MK, et al. Influence of leisure time physical activity and television watching on atherosclerosis risk factors in the NHLBI Family Heart Study. *Atherosclerosis* 2000; 153:433–443.
320. Hodgin JB, Maeda N. Minireview: estrogen and mouse models of atherosclerosis. *Endocrinology* 2002; 143:4495–4501.
321. Sowers JR. Diabetes mellitus and cardiovascular disease in women. *Arch Intern Med* 1998; 158: 617–621.
322. Rajaratnam RA, Gylling H, Miettinen TA. Cholesterol absorption, synthesis, and fecal output in postmenopausal women with and without coronary artery disease. *Arterioscler Thromb Vasc Biol* 2001; 21:1650–1655.
323. Bairey Merz CN, Johnson BD, Sharaf BL, et al.; WISE Study Group. Hypoestrogenemia of hypothalamic origin and coronary artery disease in premenopausal

- women: a report from the NHLBI-sponsored WISE study. *J Am Coll Cardiol* 2003; 41:413–419.
324. Koivu TA, Dastidar P, Jokela H, et al. The relation of oxidized LDL autoantibodies and long-term hormone replacement therapy to ultrasonographically assessed atherosclerotic plaque quantity and severity in postmenopausal women. *Atherosclerosis* 2001; 157:471–479.
325. Miller AP, Chen YF, Xing D, Feng W, Oparil S. Hormone replacement therapy and inflammation: interactions in cardiovascular disease. *Hypertension* 2003; 42:657–663.
326. Pervin S, Singh R, Rosenfeld ME, et al. Estradiol suppresses MCP-1 expression In vivo : implications for atherosclerosis. *Arterioscler Thromb Vasc Biol* 1998; 18:1575–1582.
327. Alvarez A, Hermenegildo C, Issekutz AC, Esplugues JV, Sanz MJ. Estrogens inhibit angiotensin II-induced leukocyte-endothelial cell interactions in vivo via rapid endothelial nitric oxide synthase and cyclooxygenase activation. *Circ Res* 2002; 91:1142–1150.
328. Amant C, Holm P, Xu Sh SH, et al. Estrogen receptor-mediated, nitric oxide-dependent modulation of the immunologic barrier function of the endothelium: regulation of fas ligand expression by estradiol. *Circulation* 2001; 104:2576–2581.
329. Dimitrova KR, DeGroot K, Myers AK, Kim YD. Estrogen and homocysteine. *Cardiovasc Res* 2002; 53:577–588.
330. Wagner AH, Schroeter MR, Hecker M. 17beta-estradiol inhibition of NADPH oxidase expression in human endothelial cells. *FASEB J* 2001; 15:2121–2130.
331. Murakami H, Harada N, Sasano H. Aromatase in atherosclerotic lesions of human aorta. *J Steroid Biochem Mol Biol* 2001; 79:67–74.
332. Nakamura Y, Miki Y, Suzuki T, Nakata T, Darnel AD, Moriya T, Tazawa C, Saito H, Ishibashi T, Takahashi S, Yamada S, Sasano H. Steroid sulfatase and estrogen sulfotransferase in the atherosclerotic human aorta. *Am J Pathol* 2003; 163:1329–1339.
333. Carmody BJ, Arora S, Wakefield MC, et al. Progesterone inhibits human infragenicular arterial smooth muscle cell proliferation induced by high glucose and insulin concentrations. *J Vasc Surg* 2002; 36:833–838.
334. Byington RP, Furberg CD, Herrington DM, et al.; Heart and Estrogen/Progestin Replacement Study Research Group. Effect of estrogen plus progestin on progression of carotid atherosclerosis in postmenopausal women with heart disease: HERS B-mode substudy. *Arterioscler Thromb Vasc Biol* 2002; 22:1692–1697.
335. Dwyer KM, Nordstrom CK, Bairey Merz CN, Dwyer JH. Carotid wall thickness and years since bilateral oophorectomy: the Los Angeles Atherosclerosis Study. *Am J Epidemiol* 2002; 156:438–444.
336. Uint L, Gebara OC, Pinto LB, et al. Hormone replacement therapy increases levels of antibodies against heat shock protein 65 and certain species of oxidized low density lipoprotein. *Braz J Med Biol Res* 2003; 36:491–494.
337. Barton M, Dubey RK, Traupe T. Oral contraceptives and the risk of thrombosis and atherosclerosis. *Expert Opin Investig Drugs* 2002; 11:329–332.
338. Balica M, Bostrom K, Shin V, Tillisch K, Demer LL. Calcifying subpopulation of bovine aortic smooth muscle cells is responsive to 17 beta-estradiol. *Circulation* 1997; 95:1954–1960.
339. McCrohon JA, Death AK, Nakhla S, et al. Androgen receptor expression is greater in macrophages from male than from female donors. A sex difference with implications for atherogenesis. *Circulation* 2000; 101:224–226.

340. Ide T, Tsutsui H, Ohashi N, et al. Greater oxidative stress in healthy young men compared with premenopausal women. *Arterioscler Thromb Vasc Biol* 2002; 22:438–442.
341. Golden SH, Maguire A, Ding J, et al. Endogenous postmenopausal hormones and carotid atherosclerosis: a case-control study of the atherosclerosis risk in communities cohort. *Am J Epidemiol* 2002; 155:437–445.
342. Barud W, Palusinski R, Beltowski J, Wojcicka G. Inverse relationship between total testosterone and anti-oxidized low density lipoprotein antibody levels in ageing males. *Atherosclerosis* 2002; 164:283–288.
343. De Pergola G, Pannaciuilli N, Ciccone M, et al. Free testosterone plasma levels are negatively associated with the intima-media thickness of the common carotid artery in overweight and obese glucose-tolerant young adult men. *Int J Obes Relat Metab Disord* 2003; 27:803–807.
344. Malkin CJ, Pugh PJ, Jones RD, Jones TH, Channer KS. Testosterone as a protective factor against atherosclerosis—immunomodulation and influence upon plaque development and stability. *J Endocrinol* 2003; 178:373–380.
345. Okamoto K. Distribution of dehydroepiandrosterone sulfate and relationships between its level and serum lipid levels in a rural Japanese population. *J Epidemiol* 1998; 8:285–291.
346. Savastano S, Valentino R, Belfiore A, et al. Early carotid atherosclerosis in normotensive severe obese premenopausal women with low DHEA(S). *J Endocrinol Invest* 2003; 26:236–243.
347. Boren J, Gustafsson M, Skalen K, Flood C, Innerarity TL. Role of extracellular retention of low density lipoproteins in atherosclerosis. *Curr Opin Lipidol* 2000; 11:451–456.
348. Andrews HE, Bruckderfer KR, Dunn RC et al. LDL inhibits endothelium dependent relaxation in rabbit aorta. *Nature* 1987; 327:237–239.
349. Kugiyama K, Kerns SA, Morrisett JD et al. Impairment of endothelium dependent arterial relaxation by lysolecithin in modified LDL. *Nature* 1990; 344:160–162.
350. Brown MS, Goldstein JL. Lipoprotein Metabolism in the macrophage: Implications for cholesterol deposition in atherosclerosis. *Ann Review Biochem* 1983; 52:223–261.
351. Linton MF, Babaev VR, Gleaves LA, Fazio S. A direct role for the macrophage low density lipoprotein receptor in atherosclerotic lesion formation. *J Biol Chem* 1999; 274:19204–19210.
352. Takahashi K, Takeya M, Sakashita N. Multifunctional roles of macrophages in the development and progression of atherosclerosis in humans and experimental animals. *Med Electron Microsc* 2002; 35:179–203.
353. Steinberg D, Parthasarathy S, Carew TE et al. Beyond Cholesterol. Modifications of LDL that increase its atherogenicity. *N Engl J Med* 1989; 320:915–924.
354. Palinski W, Rosenfeld ME, Yla-Herttuala S et al. LDL undergoes oxidative modification in vivo. *Proc Natl Acad Sci USA* 1989; 86:1372–1376.
355. Babaev VR, Gleaves LA, Carter KJ, et al. Reduced atherosclerotic lesions in mice deficient for total or macrophage-specific expression of scavenger receptor-A. *Arterioscler Thromb Vasc Biol* 2000; 20:2593–2599.
356. Van Eck M, De Winther MP, Herijgers N, et al. Effect of human scavenger receptor class A overexpression in bone marrow-derived cells on cholesterol levels and atherosclerosis in ApoE-deficient mice. *Arterioscler Thromb Vasc Biol* 2000; 20:2600–2606.
357. Minami M, Kume N, Shimaoka T, et al. Expression of SR-PSOX, a novel cell-surface scavenger receptor for phosphatidylserine and oxidized LDL in human atherosclerotic lesions. *Arterioscler Thromb Vasc Biol* 2001; 21:1796–1800.

358. Tanaka A, AI M, Kobayashi Y, et al. Metabolism of triglyceride-rich lipoproteins and their role in atherosclerosis. *Ann NY Acad Sci* 2001; 947:207–212; discussion 212–213.
359. Magoori K, Kang MJ, Ito MR, et al. Severe hypercholesterolemia, impaired fat tolerance, and advanced atherosclerosis in mice lacking both low density lipoprotein receptor-related protein 5 and apolipoprotein E. *J Biol Chem* 2003; 278: 11,331–11,336.
360. Boucher P, Gotthardt M, Li WP, Anderson RG, Herz J. LRP: role in vascular wall integrity and protection from atherosclerosis. *Science* 2003; 300:329–332.
361. Lindqvist P, Ostlund-Lindquist A, Witztum JL, et al. The role of LpL in the metabolism of TG-rich lipoproteins by macrophages. *J Biol Chem* 1983; 258: 9086–9092.
362. Schonfeld G, Patsch W, Pflieger B, et al. Lipolysis produces changes in the immunoreactivity and cell reactivity of VLDL. *J Clin Invest* 1979; 64:1288–1297.
363. Renier G, Skamene E, DeSanctis JB, Radzioch D. High macrophage lipoprotein lipase expression and secretion are associated in inbred murine strains with susceptibility to atherosclerosis. *Arterioscler Thromb* 1993; 13:190–196.
364. Esenabhalu VE, Cerimagic M, Malli R, et al. Tissue-specific expression of human lipoprotein lipase in the vascular system affects vascular reactivity in transgenic mice. *Br J Pharmacol* 2002; 135:143–154.
365. Dugi KA, Schmidt N, Brandauer K, et al. Activity and concentration of lipoprotein lipase in post-heparin plasma and the extent of coronary artery disease. *Atherosclerosis* 2002; 163:127–134.
366. Fan J, Unoki H, Kojima N, et al. Overexpression of lipoprotein lipase in transgenic rabbits inhibits diet-induced hypercholesterolemia and atherosclerosis. *J Biol Chem* 2001; 276:40,071–40,079.
367. de Andrade M, Thandi I, Brown S, et al. Relationship of the apolipoprotein E polymorphism with carotid artery atherosclerosis. *Am J Hum Genet* 1995; 56: 1379–1390.
368. Palinski W, Ord VA, Plump AS, et al. ApoE-deficient mice are a model of lipoprotein oxidation in atherogenesis. Demonstration of oxidation-specific epitopes in lesions and high titers of autoantibodies to malondialdehyde-lysine in serum. *Arterioscler Thromb* 1994; 14:605–616.
369. Fazio S, Babaev VR, Burleigh ME, et al. Physiological expression of macrophage apoE in the artery wall reduces atherosclerosis in severely hyperlipidemic mice. *J Lipid Res* 2002; 43:1602–1609.
370. Conde-Knape K, Bensadoun A, Sobel JH, Cohn JS, Shachter NS. Overexpression of apoC-I in apoE-null mice: severe hypertriglyceridemia due to inhibition of hepatic lipase. *J Lipid Res* 2002; 43:2136–2145.
371. Kinnunen PK, Holopainen JM. Sphingomyelinase activity of LDL: a link between atherosclerosis, ceramide, and apoptosis? *Trends Cardiovasc Med* 2002; 12:37–42.
372. Li H, Junk P, Huwiler A, et al. Dual effect of ceramide on human endothelial cells: induction of oxidative stress and transcriptional upregulation of endothelial nitric oxide synthase. *Circulation* 2002; 106:2250–2256.
373. Morel DW, DiCorleto PE, Chisolm GM. Endothelium and VSMC alter LDL in vitro by free radical oxidation. *Arteriosclerosis* 1984; 4:357–364.
374. Hulthe J, Fagerberg B. Circulating oxidized LDL is associated with subclinical atherosclerosis development and inflammatory cytokines (AIR Study). *Arterioscler Thromb Vasc Biol* 2002; 22:1162–1167.
375. Kuhn H, Heydeck D, Hugou I, Gniwotta C. In vivo action of 15-lipoxygenase in early stages of human atherogenesis. *J Clin Invest* 1997; 99:888–893.

376. Reddy MA, Kim YS, Lanting L, Natarajan R. Reduced growth factor responses in vascular smooth muscle cells derived from 12/15-lipoxygenase-deficient mice. *Hypertension* 2003; 41:1294–1300.
377. Sugiyama S, Okada Y, Sukhova GK, et al. Macrophage myeloperoxidase regulation by granulocyte macrophage colony-stimulating factor in human atherosclerosis and implications in acute coronary syndromes. *Am J Pathol* 2001; 158:879–891.
378. Heinecke JW. Tyrosyl radical production by myeloperoxidase: a phagocyte pathway for lipid peroxidation and dityrosine cross-linking of proteins. *Toxicology* 2002; 177:11–22.
379. Brennan ML, Anderson MM, Shih DM, et al. Increased atherosclerosis in myeloperoxidase-deficient mice. *J Clin Invest* 2001; 107:419–430.
380. Shimasaki H, Maeba R, Tachibana R, Ueta N. Lipid peroxidation and ceroid accumulation in macrophages cultured with oxidized low density lipoprotein. *Gerontology* 1995; 41:39–51.
381. Rueckschloss U, Duerrschmidt N, Morawietz H. NADPH oxidase in endothelial cells: impact on atherosclerosis. *Antioxid Redox Signal* 2003; 5:171–180.
382. Morawietz H, Duerrschmidt N, Niemann B, et al. Augmented endothelial uptake of oxidized low-density lipoprotein in response to endothelin-1. *Clin Sci* 2002; 103:9S–12S.
383. Rueckschloss U, Galle J, Holtz J, Zerkowski HR, Morawietz H. Induction of NAD(P)H oxidase by oxidized low-density lipoprotein in human endothelial cells: antioxidative potential of hydroxymethylglutaryl coenzyme A reductase inhibitor therapy. *Circulation* 2001; 104:1767–1772.
384. Barry-Lane PA, Patterson C, van der Merwe M, et al. p47phox is required for atherosclerotic lesion progression in ApoE(-/-) mice. *J Clin Invest* 2001; 108:1513–1522.
385. Witting P, Pettersson K, Ostlund-Lindqvist AM, et al. Dissociation of atherogenesis from aortic accumulation of lipid hydro(pero)xides in Watanabe heritable hyperlipidemic rabbits. *J Clin Invest* 1999; 104:213–220.
386. Tertov VV, Kaplun VV, Orekhov AN. In vivo oxidized low density lipoprotein: degree of lipoprotein oxidation does not correlate with its atherogenic properties. *Mol Cell Biochem* 1998; 183:141–146.
387. Hoff HF, O'Neil J, Wu Z, Hoppe G, Salomon RL. Phospholipid hydroxyalkenals: biological and chemical properties of specific oxidized lipids present in atherosclerotic lesions. *Arterioscler Thromb Vasc Biol* 2003; 23:275–282.
388. Tribble DL, Gong EL, Leeuwenburgh C, et al. Fatty streak formation in fat-fed mice expressing human copper-zinc superoxide dismutase. *Arterioscler Thromb Vasc Biol* 1997; 17:1734–1740.
389. Ferns GA, Lamb DJ, Taylor A. The possible role of copper ions in atherogenesis: the Blue Janus. *Atherosclerosis* 1997; 133:139–152.
390. Bhakdi S, Dorweiler B, Kirchmann R, et al. On the pathogenesis of atherosclerosis: enzymatic transformation of human low density lipoprotein to an atherogenic moiety. *J Exp Med* 1995; 182:1959–1971.
391. Hanasaki K, Yamada K, Yamamoto S, et al. Potent modification of low density lipoprotein by group X secretory phospholipase A2 is linked to macrophage foam cell formation. *J Biol Chem* 2002; 277:29116–29124.
392. Chen M, Masaki T, Sawamura T. LOX-1, the receptor for oxidized low-density lipoprotein identified from endothelial cells: implications in endothelial dysfunction and atherosclerosis. *Pharmacol Ther* 2002; 95: 89–100.
393. Watanabe Y, Inaba T, Gotoda T, et al. Role of macrophage colony-stimulating factor in the initial process of atherosclerosis. *Ann N Y Acad Sci* 1995; 748: 357–364; discussion 364–366.

394. Huber J, Vales A, Mitulovic G, et al. Oxidized membrane vesicles and blebs from apoptotic cells contain biologically active oxidized phospholipids that induce monocyte-endothelial interactions. *Arterioscler Thromb Vasc Biol* 2002; 22:101–107.
395. Lee C, Sigari F, Segrado T, et al. All ApoB-containing lipoproteins induce monocyte chemotaxis and adhesion when minimally modified. Modulation of lipoprotein bioactivity by platelet-activating factor acetylhydrolase. *Arterioscler Thromb Vasc Biol* 1999; 19:1437–1446.
396. Unno N, Nakamura T, Kaneko H, et al. Plasma platelet-activating factor acetylhydrolase deficiency is associated with atherosclerotic occlusive disease in Japan. *J Vasc Surg* 2000; 32:263–267.
397. Srivastava S, Liu SQ, Conklin DJ, et al. Involvement of aldose reductase in the metabolism of atherogenic aldehydes. *Chem Biol Interact* 2001; 130:563–571.
398. Kawai Y, Saito A, Shibata N, et al. Covalent binding of oxidized cholesteryl esters to protein: implications for oxidative modification of low density lipoprotein and atherosclerosis. *J Biol Chem* 2003; 278:21,040–21,049.
399. Banfi C, Camera M, Giandomenico G, et al. Vascular thrombogenicity induced by progressive LDL oxidation: protection by antioxidants. *Thromb Haemost* 2003; 89:544–553.
400. Schonbeck U, Gerdes N, Varo N, et al. Oxidized low-density lipoprotein augments and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors limit CD40 and CD40L expression in human vascular cells. *Circulation* 2002; 106:2888–2893.
401. Banfi C, Colli S, Eligini S, Mussoni L, Tremoli E. Oxidized LDLs influence thrombotic response and cyclooxygenase 2. *Prostaglandins Leukot Essent Fatty Acids* 2002; 67:169–173.
402. Webb NR, Bostrom MA, Szilvassy SJ, et al. Macrophage-expressed group IIA secretory phospholipase A2 increases atherosclerotic lesion formation in LDL receptor-deficient mice. *Arterioscler Thromb Vasc Biol* 2003; 23:263–268.
403. Burton CA, Patel S, Mundt S, et al. Deficiency in sPLA(2) does not affect HDL levels or atherosclerosis in mice. *Biochem Biophys Res Commun* 2002; 294:88–94.
404. Niessen HW, Krijnen PA, Visser CA, Meijer CJ, Erik Hack C. Type II secretory phospholipase A2 in cardiovascular disease: a mediator in atherosclerosis and ischemic damage to cardiomyocytes? *Cardiovasc Res* 2003; 60:68–77.
405. Hurt-Camejo E, Camejo G, Sartipy P. Phospholipase A2 and small, dense low-density lipoprotein. *Curr Opin Lipidol* 2000; 11:465–471.
406. Tertov VV, Kaplun VV, Sobenin IA, Orekhov AN. Low-density lipoprotein modification occurring in human plasma possible mechanism of in vivo lipoprotein desialylation as a primary step of atherogenic modification. *Atherosclerosis* 1998; 138:183–195.
407. Sobenin IA, Tertov VV, Orekhov AN. Atherogenic modified LDL in diabetes. *Diabetes* 1996; 45:S35–S39.
408. Tulenko TN, Sumner AE. The physiology of lipoproteins. *J Nucl Cardiol* 2002; 9:638–649.
409. McDowell A, Young IS, Wisdom GB. Measurement of asialylated LDL in the blood of patients with coronary artery disease by antibody-lectin sandwich assay. *Ann Clin Biochem* 2001; 38:499–508.
410. Veniant MM, Withycombe S, Young SG. Lipoprotein size and atherosclerosis susceptibility in Apoe(-/-) and Ldlr(-/-) mice. *Arterioscler Thromb Vasc Biol* 2001; 21:1567–1570.
411. Segrest JP. The role of non-LDL:non-HDL particles in atherosclerosis. *Curr Diab Rep* 2002; 2:282–288.

412. Takahashi M, Takahashi S, Shimpo M, et al. beta-very low density lipoprotein enhances inducible nitric oxide synthase expression in cytokine-stimulated vascular smooth muscle cells. *Atherosclerosis* 2002; 162:307–313.
413. Kawakami A, Tanaka A, Chiba T, et al. Remnant lipoprotein-induced smooth muscle cell proliferation involves epidermal growth factor receptor transactivation. *Circulation* 2003; 108:2679–2688.
414. Chen K, Thomas SR, Keaney JF Jr. Beyond LDL oxidation: ROS in vascular signal transduction. *Free Radic Biol Med* 2003; 35:117–132.
415. Kaneda H, Taguchi J, Ogasawara K, Aizawa T, Ohno M. Increased level of advanced oxidation protein products in patients with coronary artery disease. *Atherosclerosis* 2002; 162:221–225.
416. Harrison D, Griendling KK, Landmesser U, Hornig B, Drexler H. Role of oxidative stress in atherosclerosis. *Am J Cardiol* 2003; 91:7A–11A.
417. Fukai T, Folz RJ, Landmesser U, Harrison DG. Extracellular superoxide dismutase and cardiovascular disease. *Cardiovasc Res* 2002; 55:239–249.
418. Vassalle C, Botto N, Andreassi MG, Berti S, Biagini A. Evidence for enhanced 8-isoprostane plasma levels, as index of oxidative stress in vivo, in patients with coronary artery disease. *Coron Artery Dis* 2003; 14:213–218.
419. Schisterman EF, Faraggi D, Browne R, et al. TBARS and cardiovascular disease in a population-based sample. *J Cardiovasc Risk* 2001; 8:219–225.
420. Martinet W, Knaapen MW, De Meyer GR, Herman AG, Kockx MM. Elevated levels of oxidative DNA damage and DNA repair enzymes in human atherosclerotic plaques. *Circulation* 2002; 106:927–932.
421. Ruef J, Moser M, Kubler W, Bode C. Induction of endothelin-1 expression by oxidative stress in vascular smooth muscle cells. *Cardiovasc Pathol* 2001; 10:311–315.
422. Mashiba S, Wada Y, Takeya M, et al. In vivo complex formation of oxidized alpha(1)-antitrypsin and LDL. *Arterioscler Thromb Vasc Biol* 2001; 21:1801–1808.
423. Miyata T. Alterations of non-enzymatic biochemistry in uremia, diabetes, and atherosclerosis (“carbonyl stress”). *Bull Mem Acad R Med Belg* 2002; 157: 189–196; discussion 196–198.
424. Okuda M, Inoue N, Azumi H, et al. Expression of glutaredoxin in human coronary arteries: its potential role in antioxidant protection against atherosclerosis. *Arterioscler Thromb Vasc Biol* 2001; 21:1483–1487.
425. Meilhac O, Ramachandran S, Chiang K, Santanam N, Parthasarathy S. Role of arterial wall antioxidant defense in beneficial effects of exercise on atherosclerosis in mice. *Arterioscler Thromb Vasc Biol* 2001; 21:1681–1688.
426. D’Armiento FP, Bianchi A, de Nigris F, et al. Age-related effects on atherogenesis and scavenger enzymes of intracranial and extracranial arteries in men without classic risk factors for atherosclerosis. *Stroke* 2001; 32:2472–2479.
427. Blanc J, Alves-Guerra MC, Esposito B, et al. Protective role of uncoupling protein 2 in atherosclerosis. *Circulation* 2003; 107:388–390.
428. Napoli C, Martin-Padura I, de Nigris F, et al. Deletion of the p66Shc longevity gene reduces systemic and tissue oxidative stress, vascular cell apoptosis, and early atherogenesis in mice fed a high-fat diet. *Proc Natl Acad Sci USA* 2003; 100: 2112–2116.
429. Jiang XC. The effect of phospholipid transfer protein on lipoprotein metabolism and atherosclerosis. *Front Biosci* 2002; 7:d1634–d1641.
430. O’Brien KD, Vuletic S, McDonald TO, et al. Cell-associated and extracellular phospholipid transfer protein in human coronary atherosclerosis. *Circulation* 2003; 108:270–274.

431. Chiwata T, Aragane K, Fujinami K, et al. Direct effect of an acyl-CoA:cholesterol acyltransferase inhibitor, F-1394, on atherosclerosis in apolipoprotein E and low density lipoprotein receptor double knockout mice. *Br J Pharmacol* 2001; 133:1005–1012.
432. Sakashita N, Miyazaki A, Chang CC, et al. Acyl-coenzyme A:cholesterol acyltransferase 2 (ACAT2) is induced in monocyte-derived macrophages: in vivo and in vitro studies. *Lab Invest* 2003; 83:1569–1581.
433. Willner EL, Tow B, Buhman KK, et al. Deficiency of acyl CoA:cholesterol acyltransferase 2 prevents atherosclerosis in apolipoprotein E-deficient mice. *Proc Natl Acad Sci USA* 2003; 100:1262–1267.
434. Auge N, Rebai O, Lepetit-Thevenin J, et al. Pancreatic bile salt-dependent lipase induces smooth muscle cells proliferation. *Circulation* 2003; 108:86–91.
435. Hui DY, Howles PN. Carboxyl ester lipase: structure–function relationship and physiological role in lipoprotein metabolism and atherosclerosis. *J Lipid Res* 2002; 43:2017–2030.
436. Trougakos IP, Poulakou M, Stathatos M, et al. Serum levels of the senescence biomarker clusterin/apolipoprotein J increase significantly in diabetes type II and during development of coronary heart disease or at myocardial infarction. *Exp Gerontol* 2002; 37:1175–1187.
437. Gonzalez-Navarro H, Nong Z, Freeman L, et al. Identification of mouse and human macrophages as a site of synthesis of hepatic lipase. *J Lipid Res* 2002; 43:671–675.
438. Dugi KA, Brandauer K, Schmidt N, et al. Low hepatic lipase activity is a novel risk factor for coronary artery disease. *Circulation* 2001; 104:3057–3062.
439. Okazaki H, Osuga J, Tsukamoto K, et al. Elimination of cholesterol ester from macrophage foam cells by adenovirus-mediated gene transfer of hormone-sensitive lipase. *J Biol Chem* 2002; 277:31,893–31,899.
440. Argmann CA, Van Den Diepstraten CH, Sawyez CG, et al. Transforming growth factor-beta1 inhibits macrophage cholesteryl ester accumulation induced by native and oxidized VLDL remnants. *Arterioscler Thromb Vasc Biol* 2001; 21: 2011–2018.
441. Kiechl S, Willeit J, Egger G, Poewe W, Oberhollenzer F. Body iron stores and the risk of carotid atherosclerosis: prospective results from the Bruneck study. *Circulation* 1997; 96:3300–3307.
442. Moore M, Folsom AR, Barnes RW, Eckfeldt JH. No association between serum ferritin and asymptomatic carotid atherosclerosis. The Atherosclerosis Risk in Communities (ARIC) Study. *Am J Epidemiol* 1995; 141:719–723.
443. Dabbagh AJ, Shwaery GT, Keane JF Jr, Frei B. Effect of iron overload and iron deficiency on atherosclerosis in the hypercholesterolemic rabbit. *Arterioscler Thromb Vasc Biol* 1997; 17:2638–2645.
444. Utermann G. The mysteries of Lp (a). *Science* 1989; 246:904–910.
445. Nachman RL. Thrombosis and atherogenesis: Molecular Connections. *Blood* 1992; 79:1897–1906.
446. Schreiner PJ. Lipoprotein(a) as a risk factor for preclinical atherosclerotic disease in a biracial cohort: the Atherosclerosis Risk in Communities (ARIC) Study. *Chem Phys Lipids* 1994; 67:405–410.
447. Baldassarre D, Tremoli E, Franceschini G, Michelagnoli S, Sirtori CR. Plasma lipoprotein(a) is an independent factor associated with carotid wall thickening in severely but not moderately hypercholesterolemic patients. *Stroke* 1996; 27: 1044–1049.
448. Berg K, Svindland A, Smith AJ, et al. Spontaneous atherosclerosis in the proximal aorta of LPA transgenic mice on a normal diet. *Atherosclerosis* 2002; 163:99–104.

449. Fu L, Jamieson DG, Usher DC, Lavi E. Gene expression of apolipoprotein(a) within the wall of human aorta and carotid arteries. *Atherosclerosis* 2001; 158:303–311.
450. Scanu AM. Lipoprotein(a) and the atherothrombotic process: mechanistic insights and clinical implications. *Curr Atheroscler Rep* 2003; 5:106–113.
451. Komai N, Morishita R, Yamada S, et al. Mitogenic activity of oxidized lipoprotein (a) on human vascular smooth muscle cells. *Hypertension* 2002; 40:310–314.
452. Allen S, Khan S, Tam Sp, et al. Expression of adhesion molecules by lp(a): a potential novel mechanism for its atherogenicity. *FASEB J* 1998; 12:1765–1776.
453. Buechler C, Ullrich H, Aslanidis C, et al. Lipoprotein (a) downregulates lysosomal acid lipase and induces interleukin-6 in human blood monocytes. *Biochim Biophys Acta* 2003; 1642:25–31.
454. Kostner KM, Kostner GM. Lipoprotein(a): still an enigma? *Curr Opin Lipidol* 2002; 13:391–396.
455. Loscalzo J. Lipoprotein (a): a unique risk factor for atherothrombotic disease. *Arteriosclerosis* 1990; 10:672–679.
456. Dahlen GH. Indications of an autoimmune component in LP(a) associated disorders. *Eur J Immunogenet* 1994; 21:301–312.
457. Scanu AM. Lp (a): Its inheritance and molecular basis of its atherothrombotic role. *Mol Cell Biochem* 1992; 113:127–131.
458. Lippi G, Guidi G. Lipoprotein(a): an emerging cardiovascular risk factor. *Crit Rev Clin Lab Sci* 2003; 40:1–42.
459. Burchfiel CM, Laws A, Benfante R, et al. Combined effects of HDL cholesterol, triglyceride, and total cholesterol concentrations on 18-year risk of atherosclerotic disease. *Circulation* 1995; 92:1430–1436.
460. Rong JX, Li J, Reis ED, et al. Elevating high-density lipoprotein cholesterol in apolipoprotein E-deficient mice remodels advanced atherosclerotic lesions by decreasing macrophage and increasing smooth muscle cell content. *Circulation* 2001; 104:2447–2452.
461. Dionyssiou-Asteriou A, Papastamatiou M, Vatalas IA, Bastounis E. Serum apolipoprotein AI levels in atherosclerotic and diabetic patients. *Eur J Vasc Endovasc Surg* 2002; 24:161–165.
462. Schultz JR, Verstuyft JG, Gong EL, Nichols AV, Rubin EM. Protein composition determines the anti-atherogenic properties of HDL in transgenic mice. *Nature* 1993; 365:762–764.
463. Fruchart JC, De Geteire C, Delfly B, Castro GR. Apolipoprotein A-I-containing particles and reverse cholesterol transport: evidence for connection between cholesterol efflux and atherosclerosis risk. *Atherosclerosis* 1994; 110:S35–S39.
464. Major AS, Dove DE, Ishiguro H, et al. Increased cholesterol efflux in apolipoprotein AI (ApoAI)-producing macrophages as a mechanism for reduced atherosclerosis in ApoAI(–/–) mice. *Arterioscler Thromb Vasc Biol* 2001; 21:1790–1795.
465. Ishiguro H, Yoshida H, Major AS, et al. Retrovirus-mediated expression of apolipoprotein A-I in the macrophage protects against atherosclerosis in vivo. *J Biol Chem* 2001; 276:36,742–36,748.
466. Marotti KR, Castle CK, Boyle TP, et al. Severe atherosclerosis in transgenic mice expressing simian cholesteryl ester transfer protein. *Nature* 1993; 364:73–75.
467. Barter PJ, Brewer HB Jr, Chapman MJ, et al. Cholesteryl ester transfer protein: a novel target for raising HDL and inhibiting atherosclerosis. *Arterioscler Thromb Vasc Biol* 2003; 23:160–167.
468. Huang Z, Inazu A, Nohara A, Higashikata T, Mabuchi H. Cholesteryl ester transfer protein inhibitor (JTT-705) and the development of atherosclerosis in rabbits with severe hypercholesterolaemia. *Clin Sci* 2002; 103:587–594.

469. Zhang Z, Yamashita S, Hirano K, et al. Expression of cholesteryl ester transfer protein in human atherosclerotic lesions and its implication in reverse cholesterol transport. *Atherosclerosis* 2001; 159:67–75.
470. Furbee JW Jr, Sawyer JK, Parks JS. Lecithin:cholesterol acyltransferase deficiency increases atherosclerosis in the low density lipoprotein receptor and apolipoprotein E knockout mice. *J Biol Chem* 2002; 277:3511–3519.
471. Ng DS, Maguire GF, Wylie J, et al. Oxidative stress is markedly elevated in lecithin:cholesterol acyltransferase-deficient mice and is paradoxically reversed in the apolipoprotein E knockout background in association with a reduction in atherosclerosis. *J Biol Chem* 2002; 277:11,715–11,720.
472. Tailleux A, Duriez P, Fruchart JC, Clavey V. Apolipoprotein A-II, HDL metabolism and atherosclerosis. *Atherosclerosis* 2002; 164:1–13.
473. Blanco-Vaca F, Escola-Gil JC, Martin-Campos JM, Julve J. Role of apoA-II in lipid metabolism and atherosclerosis: advances in the study of an enigmatic protein. *J Lipid Res* 2001; 42:1727–1739.
474. Owen JS, Mulcahy JV. ATP-binding cassette A1 protein and HDL homeostasis. *Atheroscler Suppl* 2002; 3:13–22.
475. Brousseau ME. ATP-binding cassette transporter A1, fatty acids, and cholesterol absorption. *Curr Opin Lipidol* 2003; 14:35–40.
476. Feng B, Tabas I. ABCA1-mediated cholesterol efflux is defective in free cholesterol-loaded macrophages. Mechanism involves enhanced ABCA1 degradation in a process requiring full NPC1 activity. *J Biol Chem* 2002; 277:43,271–43,280.
477. van Dam MJ, de Groot E, Clee SM, et al. Association between increased arterial-wall thickness and impairment in ABCA1-driven cholesterol efflux: an observational study. *Lancet* 2002; 359:37–42.
478. Singaraja RR, Fievet C, Castro G, et al. Increased ABCA1 activity protects against atherosclerosis. *J Clin Invest* 2002; 110:35–42.
479. Aiello RJ, Brees D, Bourassa PA, et al. Increased atherosclerosis in hyperlipidemic mice with inactivation of ABCA1 in macrophages. *Arterioscler Thromb Vasc Biol* 2002; 22:630–637.
480. Van Eck M, Twisk J, Hoekstra M, et al. Differential effects of scavenger receptor BI deficiency on lipid metabolism in cells of the arterial wall and in the liver. *J Biol Chem* 2003; 278:23,699–23,705.
481. Hullinger TG, Panek RL, Xu X, Karathanasis SK. p21-activated kinase-1 (PAK1) inhibition of the human scavenger receptor class B, type I promoter in macrophages is independent of PAK1 kinase activity, but requires the GTPase-binding domain. *J Biol Chem* 2001; 276:46,807–46,814.
482. Sharma N, Desigan B, Ghosh S, et al. The role of oxidized HDL in monocyte/macrophage functions in the pathogenesis of atherosclerosis in Rhesus monkeys. *Scand J Clin Lab Invest* 1999; 59:215–225.
483. Mackness B, Durrington PN, Mackness MI. The paraoxonase gene family and coronary heart disease. *Curr Opin Lipidol* 2002; 13:357–362.
484. Mackness B, Davies GK, Turkie W, et al. Paraoxonase status in coronary heart disease: are activity and concentration more important than genotype? *Arterioscler Thromb Vasc Biol* 2001; 21:1451–1457.
485. Shih DM, Gu L, Hama S, et al. Genetic-dietary regulation of serum paraoxonase expression and its role in atherogenesis in a mouse model. *J Clin Invest* 1996; 97:1630–1639.
486. Mackness M, Boullier A, Hennuyer N, et al. Paraoxonase activity is reduced by a pro-atherosclerotic diet in rabbits. *Biochem Biophys Res Commun* 2000; 269:232–236.

487. Tward A, Xia YR, Wang XP, et al. Decreased atherosclerotic lesion formation in human serum paraoxonase transgenic mice. *Circulation* 2002; 106:484–490.
488. Rozenberg O, Shih DM, Aviram M. Human serum paraoxonase 1 decreases macrophage cholesterol biosynthesis: possible role for its phospholipase-A2-like activity and lysophosphatidylcholine formation. *Arterioscler Thromb Vasc Biol* 2003; 23:461–467.
489. Rosenblat M, Draganov D, Watson CE, et al. Mouse macrophage paraoxonase 2 activity is increased whereas cellular paraoxonase 3 activity is decreased under oxidative stress. *Arterioscler Thromb Vasc Biol* 2003; 23:468–474.
490. Esterbauer H, Puhl H, Diber-Rotheneder M et al. Effects of antioxidants on oxidative modification of LDL. *Ann Med* 1991; 23:573–581.
491. Rasmussen HS, Aurup P, Goldstein K et al. Influence of Mg substitution therapy on blood lipid composition in patients with Ischemic Heart Disease. *Arch Intern Med* 1989; 149:1050–1053.
492. Benlian P, De Gennes JL, Foubert L, et al. Premature atherosclerosis in patients with familial chylomicronemia caused by mutations in the lipoprotein lipase gene. *N Engl J Med* 1996; 335:848–854.
493. Reymer PW, Gagne E, Groenemeyer BE, et al. A lipoprotein lipase mutation (Asn291Ser) is associated with reduced HDL cholesterol levels in premature atherosclerosis. *Nat Genet* 1995; 10:28–34.
494. Ishimoto Y, Yamada K, Yamamoto S, et al. Group V and X secretory phospholipase A(2)s-induced modification of high-density lipoprotein linked to the reduction of its antiatherogenic functions. *Biochim Biophys Acta* 2003; 1642:129–138.
495. Choi SY, Hirata K, Ishida T, Quertermous T, Cooper AD. Endothelial lipase: a new lipase on the block. *J Lipid Res* 2002; 43:1763–1769.
496. Ma K, Cilingiroglu M, Otvos JD, et al. Endothelial lipase is a major genetic determinant for high-density lipoprotein concentration, structure, and metabolism. *Proc Natl Acad Sci USA* 2003; 100:2748–2753.
497. Jin W, Sun GS, Marchadier D, et al. Endothelial cells secrete triglyceride lipase and phospholipase activities in response to cytokines as a result of endothelial lipase. *Circ Res* 2003; 92:644–650.
498. Miyake JH, Duong-Polk XT, Taylor JM, et al. Transgenic expression of cholesterol-7-alpha-hydroxylase prevents atherosclerosis in C57BL/6J mice. *Arterioscler Thromb Vasc Biol* 2002; 22:121–126.
499. Nofer JR, Kehrel B, Fobker M, et al. HDL and arteriosclerosis: beyond reverse cholesterol transport. *Atherosclerosis* 2002; 161:1–16.
500. Calabresi L, Gomaschi M, Franceschini G. Endothelial protection by high-density lipoproteins: from bench to bedside. *Arterioscler Thromb Vasc Biol* 2003; 23:1724–1731.
501. Millatt LJ, Bocher V, Fruchart JC, Staels B. Liver X receptors and the control of cholesterol homeostasis: potential therapeutic targets for the treatment of atherosclerosis. *Biochim Biophys Acta* 2003; 1631:107–118.
502. Joseph SB, Castrillo A, Laffitte BA, Mangelsdorf DJ, Tontonoz P. Reciprocal regulation of inflammation and lipid metabolism by liver X receptors. *Nat Med* 2003; 9:213–219.
503. Tangirala RK, Bischoff ED, Joseph SB, et al. Identification of macrophage liver X receptors as inhibitors of atherosclerosis. *Proc Natl Acad Sci USA* 2002; 99:11,896–11,901.
504. Schuster GU, Parini P, Wang L, et al. Accumulation of foam cells in liver X receptor-deficient mice. *Circulation* 2002; 106:1147–1153.

505. Laffitte BA, Joseph SB, Chen M, et al. The phospholipid transfer protein gene is a liver X receptor target expressed by macrophages in atherosclerotic lesions. *Mol Cell Biol* 2003; 23:2182–2191.
506. Castrillo A, Joseph SB, Marathe C, Mangelsdorf DJ, Tontonoz P. Liver X receptor-dependent repression of matrix metalloproteinase-9 expression in macrophages. *J Biol Chem* 2003; 278:10,443–10,449.
507. Barbier O, Torra IP, Duguay Y, et al. Pleiotropic actions of peroxisome proliferator-activated receptors in lipid metabolism and atherosclerosis. *Arterioscler Thromb Vasc Biol* 2002; 22:717–726.
508. Malerod L, Sporstol M, Juvet LK, et al. Hepatic scavenger receptor class B, type I is stimulated by peroxisome proliferator-activated receptor gamma and hepatocyte nuclear factor 4alpha. *Biochem Biophys Res Commun* 2003; 305:557–565.
509. Chinetti G, Lestavel S, Fruchart JC, Clavey V, Staels B. Peroxisome proliferator-activated receptor alpha reduces cholesterol esterification in macrophages. *Circ Res* 2003; 92:212–217.
510. Sugawara A, Uruno A, Kudo M, et al. Transcription suppression of thromboxane receptor gene by peroxisome proliferator-activated receptor-gamma via an interaction with Sp1 in vascular smooth muscle cells. *J Biol Chem* 2002; 277:9676–9683.
511. Fu M, Zhu X, Wang Q, et al. Platelet-derived growth factor promotes the expression of peroxisome proliferator-activated receptor gamma in vascular smooth muscle cells by a phosphatidylinositol 3-kinase/Akt signaling pathway. *Circ Res* 2001; 89:1058–1064.
512. Li L, Beauchamp MC, Renier G. Peroxisome proliferator-activated receptor alpha and gamma agonists upregulate human macrophage lipoprotein lipase expression. *Atherosclerosis* 2002; 165:101–110.
513. Lee CH, Chawla A, Urbiztondo N, et al. Transcriptional repression of atherogenic inflammation: modulation by PPARdelta. *Science* 2003; 302:453–457. Erratum in: *Science* 2003; 302:1153.
514. Layne MD, Patel A, Chen YH, et al. Role of macrophage-expressed adipocyte fatty acid binding protein in the development of accelerated atherosclerosis in hypercholesterolemic mice. *FASEB J* 2001; 15:2733–2735.
515. Fu Y, Luo N, Lopes-Virella MF, Garvey WT. The adipocyte lipid binding protein (ALBP/aP2) gene facilitates foam cell formation in human THP-1 macrophages. *Atherosclerosis* 2002; 165:259–269.
516. Bruemmer D, Collins AR, Noh G, et al. Angiotensin II-accelerated atherosclerosis and aneurysm formation is attenuated in osteopontin-deficient mice. *J Clin Invest* 2003; 112:1318–1331.
517. Scott L, Kerr A, Haydock D, Merrilees M. Subendothelial proteoglycan synthesis and transforming growth factor beta distribution correlate with susceptibility to atherosclerosis. *J Vasc Res* 1997; 34:365–377.
518. Isoda K, Nishikawa K, Kamezawa Y, et al. Osteopontin plays an important role in the development of medial thickening and neointimal formation. *Circ Res* 2002; 91:77–82.
519. Chiba S, Okamoto H, Kon S, et al. Development of atherosclerosis in osteopontin transgenic mice. *Heart Vessels* 2002; 16:111–117.
520. Kwak BR, Veillard N, Pelli G, et al. Reduced connexin43 expression inhibits atherosclerotic lesion formation in low-density lipoprotein receptor-deficient mice. *Circulation* 2003; 107:1033–1039.
521. Frank PG, Lee H, Park DS, et al. Genetic Ablation of Caveolin-1 Confers Protection Against Atherosclerosis. *Arterioscler Thromb Vasc Biol* 2004; 24:98–105.

522. Plenz GA, Deng MC, Robenek H, Volker W. Vascular collagens: spotlight on the role of type VIII collagen in atherogenesis. *Atherosclerosis* 2003; 166:1–11.
523. Onda M, Ishiwata T, Kawahara K, et al. Expression of lumican in thickened intima and smooth muscle cells in human coronary atherosclerosis. *Exp Mol Pathol* 2002; 72:142–149.
524. Theocharis AD, Theocharis DA, De Luca G, Hjerpe A, Karamanos NK. Compositional and structural alterations of chondroitin and dermatan sulfates during the progression of atherosclerosis and aneurysmal dilatation of the human abdominal aorta. *Biochimie* 2002; 84:667–674.
525. Chait A, Wight TN. Interaction of native and modified low-density lipoproteins with extracellular matrix. *Curr Opin Lipidol* 2000; 11:457–463.
526. Skalen K, Gustafsson M, Rydberg EK, et al. Subendothelial retention of atherogenic lipoproteins in early atherosclerosis. *Nature* 2002; 417:750–754.
527. Camejo G, Olsson U, Hurt-Camejo E, Baharamian N, Bondjers G. The extracellular matrix on atherogenesis and diabetes-associated vascular disease. *Atheroscler Suppl* 2002; 3:3–9.
528. Galis ZS, Khatri JJ. Matrix metalloproteinases in vascular remodeling and atherogenesis: the good, the bad, and the ugly. *Circ Res* 2002; 90:251–262.
529. Jones CB, Sane DC, Herrington DM. Matrix metalloproteinases. A review of their structure and role in acute coronary syndrome. *Cardiovasc Res* 2003; 59:812–823.
530. Herman MP, Sukhova GK, Kisiel W, et al. Tissue factor pathway inhibitor-2 is a novel inhibitor of matrix metalloproteinases with implications for atherosclerosis. *J Clin Invest* 2001; 107:1117–1126.
531. Joseph J, Ranganathan S, Mehta JL. Low density lipoproteins modulate collagen metabolism in fibroblasts. *J Cardiovasc Pharmacol Ther* 2003; 8:161–166.
532. Lemaitre V, O'Byrne TK, Borczuk AC, et al. ApoE knockout mice expressing human matrix metalloproteinase-1 in macrophages have less advanced atherosclerosis. *J Clin Invest* 2001; 107:1227–1234.
533. Galis ZS, Johnson C, Godin D, et al. Targeted disruption of the matrix metalloproteinase-9 gene impairs smooth muscle cell migration and geometrical arterial remodeling. *Circ Res* 2002; 91:852–859.
534. Kalela A, Koivu TA, Sisto T, et al. Serum matrix metalloproteinase-9 concentration in angiographically assessed coronary artery disease. *Scand J Clin Lab Invest* 2002; 62:337–342.
535. Saito S, Zempo N, Yamashita A, et al. Matrix metalloproteinase expressions in arteriosclerotic aneurysmal disease. *Vasc Endovascular Surg* 2002; 36:1–7.
536. Jormsjo S, Wuttge DM, Sirsjo A, et al. Differential expression of cysteine and aspartic proteases during progression of atherosclerosis in apolipoprotein E-deficient mice. *Am J Pathol* 2002; 161:939–945.
537. Sukhova GK, Zhang Y, Pan JH, et al. Deficiency of cathepsin S reduces atherosclerosis in LDL receptor-deficient mice. *J Clin Invest* 2003; 111:897–906.
538. Silence J, Lupu F, Collen D, Lijnen HR. Persistence of atherosclerotic plaque but reduced aneurysm formation in mice with stromelysin-1 (MMP-3) gene inactivation. *Arterioscler Thromb Vasc Biol* 2001; 21:1440–1445.
539. Cipollone F, Prontera C, Pini B, et al. Overexpression of functionally coupled cyclooxygenase-2 and prostaglandin E synthase in symptomatic atherosclerotic plaques as a basis of prostaglandin E(2)-dependent plaque instability. *Circulation* 2001; 104:921–927.
540. Watson KE, Parhami F, Shin V, Demer LL. Fibronectin and collagen I matrixes promote calcification of vascular cells in vitro, whereas collagen IV matrix is inhibitory. *Arterioscler Thromb Vasc Biol* 1998; 18:1964–1971.

541. Hunt JL, Fairman R, Mitchell ME, et al. Bone formation in carotid plaques: a clinicopathological study. *Stroke* 2002; 33:1214–1219.
542. Dhore CR, Cleutjens JP, Lutgens E, et al. Differential expression of bone matrix regulatory proteins in human atherosclerotic plaques. *Arterioscler Thromb Vasc Biol* 2001; 21:1998–2003.
543. Schoppet M, Sattler AM, Schaefer JR, et al. Increased osteoprotegerin serum levels in men with coronary artery disease. *J Clin Endocrinol Metab* 2003; 88:1024–1028.
544. Fitzpatrick LA, Turner RT, Ritman ER. Endochondral bone formation in the heart: a possible mechanism of coronary calcification. *Endocrinology* 2003; 144: 2214–2219.
545. Sun H, Unoki H, Wang X, et al. Lipoprotein(a) enhances advanced atherosclerosis and vascular calcification in WHHL transgenic rabbits expressing human apolipoprotein(a). *J Biol Chem* 2002; 277:47,486–47,492.
546. Parhami F, Basseri B, Hwang J, Tintut Y, Demer LL. High-density lipoprotein regulates calcification of vascular cells. *Circ Res* 2002; 91:570–576.
547. Shioi A, Katagi M, Okuno Y, et al. Induction of bone-type alkaline phosphatase in human vascular smooth muscle cells: roles of tumor necrosis factor- α and oncostatin M derived from macrophages. *Circ Res* 2002; 91:9–16.
548. Takayama K, Garcia-Cardena G, Sukhova GK, et al. Prostaglandin E2 suppresses chemokine production in human macrophages through the EP4 receptor. *J Biol Chem* 2002; 277:44,147–44,154.

9

Lower Extremity Arterial Disease Co-Existing With Coronary Artery Disease

*Dennis G. Caralis, MD, PhD, MPH,
FAHA, FACC*

CONTENTS

INTRODUCTION
RISK FACTORS OF LEAD CO-EXISTING
WITH CORONARY ARTERY DISEASE
OTHER THAN OVER 40 YEARS OF AGE
WHAT DO PATIENTS WITH LOWER EXTREMITY
ARTERIAL DISEASE ASSESSED WITH A LOW
ANKLE-BRACHIAL INDEX DIE FROM?
DOBUTAMINE STRESS ECHOCARDIOGRAPHY
MANAGEMENT
EXTRA-LOW LDL CHOLESTEROL
WHAT IS THE SIGNIFICANCE
OF LOW HDL CHOLESTEROL?
EFFECTS OF NIACIN
REFERENCES

INTRODUCTION

The most common risk factor for both disease entities is age; older than 40 years of age for men and older than 50 years of age for women. As the population ages, the prevalence of coronary artery disease (CAD), lower extremity arterial disease (LEAD), carotid disease, and overall cardiovascular disease increases (Fig. 1).

From: *Lower Extremity Arterial Disease*
Edited by: D. G. Caralis and G. L. Bakris © Humana Press Inc., Totowa, NJ

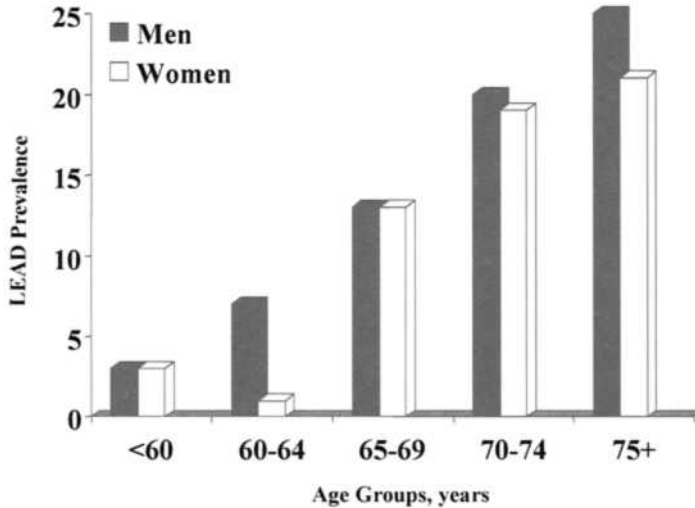


Fig. 1. The increased prevalence of LEAD in men and women with advancing age. (Reprinted from ref. 36 with permission from the Society for Vascular Surgery and the American Association for Vascular Surgery.)

RISK FACTORS OF LEAD CO-EXISTING WITH CORONARY ARTERY DISEASE OTHER THAN OVER 40 YEARS OF AGE

- Obesity, as measured by the body mass index (BMI), is a risk factor for both moderate and severe LEAD and coronary heart disease (CHD) (1,2). It should be noted that approximately 90% of obese patients with moderate LEAD (1) are claudication free.
- Cigaret smoking as measured by the number of packs/years is the most prevalent risk factor for CAD and severe LEAD (3). Of patients with severe LEAD, 72.2% are asymptomatic (1).
- Significant associations ($p < 0.05$) exist between:
- Elevated serum triglycerides and LEAD (4).
 - Systolic and diastolic hypertension and LEAD (4).
 - In men, elevated fasting blood glucose is a significant risk factor for LEAD (4-6).
- Low serum values of high-density lipoprotein cholesterol (HDL-C) are an important risk factor for CAD and severe LEAD (4,7,8). In men, low blood levels of HDL are found in very symptomatic patients with disabling intermittent claudication.
- Physical inactivity causes low HDL levels and low HDL is a risk factor for symptomatic LEAD and for CHD (9).

Table 1
Risk Factors for LEAD Co-Existing With CAD

Modifiable
• Smoking
• Diabetes
• Obesity
• Hypertension
• Dyslipidemia
• Hyperhomocysteinemia
Nonmodifiable
• Advanced age
• Male gender
• Postmenopausal
• Positive family history

- Diabetes mellitus is the strongest risk factor for LEAD (4,10) in tandem with cigaret smoking (3,4). Elevated low-density lipoprotein cholesterol (LDL-C) alone is not a separate risk factor for LEAD, but it is for CAD (11) (Table 1).
- The combination of hypertriglyceridemia with low HDL and decreased LDL-C particle size is a dislipidemia known as *pattern B* dislipidemia. In pattern B dislipidemia the most important role in atherogenesis leading to LEAD is played by the high level of triglycerides (4,12). Another type of dislipidemia is encountered in syndrome X, characterized by high triglycerides and low HDL. Aggression (aggressive personality) has also been associated with LEAD and CAD (12).
- In (dis)metabolic syndrome X (Table 2) insulin resistance plays a pivotal role for the development of diabetes mellitus, hypertriglyceridemia, and LEAD.

Other risk factors for both LEAD and CAD are:

- Apolipoprotein B level; taken as a single measurement, the apolipoprotein B level alerts the clinician on the number of potentially atherogenic particles (13).
- High lipoprotein (a) [Lp(a)] (14–17). There is no effective pharmacologic agent to significantly reduce the high Lp(a) level; niacin has a modest effect—an effective strategy is to keep the LDL-C very low. This approach markedly reduces the atherogenic effects of elevated Lp(a) (18). Lp(a) is a lipid particle similar to LDL with an additional attached glycoprotein apoprotein (a), which has been associated with premature atherosclerosis and thrombosis (19). A trial comparing the effects of statin therapy alone vs combination therapy with apheresis and statin to lower Lp(a) showed that Lp(a) is an independent risk factor

Table 2
Diagnostic Criteria for Metabolic Syndrome

<i>Feature</i>	<i>Criterion*</i>
Abdominal girth	Waist circumference
Men	>102 cm (40 in)
Women	>88 cm (35 in)
Fasting plasma HDL-C	
Men	<40 mg/dL (1.03 mmol/L)
Women	<50 mg/dL (1.29 mmol/L)
Fasting plasma triglycerides	≥150 mg/dL (1.69 mmol/L)
Fasting blood glucose	≥110 mg/dL (6.1 mmol/L)
Blood pressure	≥130/85 mm Hg

HDL-C, high-density lipoprotein cholesterol.

*A diagnosis of metabolic syndrome is made if a patient has three or more of the criteria listed.

Adapted from Adult Treatment Panel III (11).

for the development of LEAD (20). Combination treatment of apheresis and statin resulted in a significant reduction in serum Lp(a) compared to statin therapy alone, which lowered LDL-C, but not Lp(a). After 2 years, there was a significant reduction in the number of new peripheral arterial stenoses measured by duplex ultrasonography in the patients receiving apheresis (21) combined with statin therapy compared with the group on statin alone. Elevated Lp(a) calls for an aggressive reduction of LDL-C as low as possible in patients with LEAD and CAD.

- Elevated serum homocysteine (22–26). High serum homocysteine is an independent risk factor for LEAD; it also increases cardiovascular mortality (22). Homocysteine causes the formation of reactive oxygen species, and thus promotes endothelial dysfunction, proliferation of smooth muscle cells of the arterial wall, and accelerates atherosclerosis (22).
- Elevated fibrinogen (27–29). There is laboratory variability in fibrinogen assessment and, on the other hand, fibrinogen is an acute phase reactant. Smoke cessation decreases fibrinogen levels. It is also worth emphasizing that vigorous physical exercise promotes fibrinolytic activity.
- Fibrinogen genotype (30,31).
- High blood viscosity (32).
- Inflammatory processes, associated with elevated biomarkers, like high sensitivity C-reactive protein (CRP) and interleukin (IL)-6 that induces the expression and release of CRP (33–35). Indeed, inflammation characterizes all phases of atherosclerosis

The prevalence of LEAD coexisting with CAD depends on the populations screened and the methodology used. Intermittent claudication alone, which is a clinical diagnosis based on symptoms, cannot be relied upon for the accurate detection of LEAD. Noninvasive testing is essential—like the ankle-brachial index (ABI), which is a simple, accurate, inexpensive, and a noninvasive method. The prevalence of LEAD increases with age; from less than 3% below the age of 60 years to more than 20% at age 75 and older (36). The majority of patients over the age of 75 with LEAD are claudication free. Overall, risk factors for LEAD are very similar to those for CAD. Cigaret smoking, diabetes mellitus, and/or insulin resistance are not only risk factors, but also prognosticators for the development of LEAD. There is a great deal of correlation between survival and LEAD severity (37,38).

The ABI can be used not only to diagnose accurately, simply, and noninvasively LEAD, but also assesses prognosis (39). The worst prognosis was found in patients with ABI of less than 0.4 (40). There is a close correlation between LEAD severity and mortality during a 10-year period (41). The ABI used to diagnose LEAD or make a prognosis for survival is the lower of the two, left or right ankle. The severity of LEAD is closely associated with the risk for myocardial infarction (MI), ischemic stroke, and cardiovascular mortality in both symptomatic and asymptomatic patients. The lower the ABI, the higher the risk for cardiovascular events (37,38). More than 50% of patients diagnosed to have LEAD by low ABI have no typical symptoms (37,38). In the Systolic Hypertension in the Elderly Program (SHEP) study (42,43), an adjusted relative risk of 2.5 was found when cardiovascular disease morbidity and mortality were examined in subjects with LEAD, defined as an ABI of less than 0.9. All of the subjects in the SHEP study had isolated systolic hypertension and were randomized to receive antihypertensive therapy (42,43). Using age and gender matched populations of normal individuals and patients with intermittent claudication, Jelnes and coworkers (44) tracked subject survival for more than 7 years. Mortality among patients with intermittent claudication was 44%, about twice that of controls (44). In a large multicenter clinical trial performed in Italy, 2111 consecutive patients with LEAD were examined to identify predictors of cardiovascular events (45). The data were analyzed as a prospective, observational, epidemiological study. Factors that increased the risk of cardiovascular events in patients with LEAD were evaluated in a multivariate analysis (45). Hypertension (45,46), a low ABI, and cigarette smoking independently increase the risk of cardiovascular events, as does a history of vascular surgery, that by itself can be considered as a marker of disease severity. Elevated white blood cell count and high

plasma fibrinogen levels are also independent predictors of cardiovascular events in patients with LEAD (27,45).

WHAT DO PATIENTS WITH LOWER EXTREMITY ARTERIAL DISEASE ASSESSED WITH A LOW ANKLE-BRACHIAL INDEX DIE FROM?

Cardiovascular mortality can be predicted based on the low ABI (47). Compared to those with normal ABI, patients with LEAD die from CAD or cerebrovascular disease (48–50). Patients with LEAD have a fourfold risk of dying from CAD. Moreover, LEAD can be used as a prognosticator of mortality in coronary patients treated medically or with coronary artery bypass grafting (CABG) (45,48,49) or percutaneous coronary intervention (PCI) (45,48,49,51). There is a graded correlation between survival and LEAD severity in patients with severe and symptomatic LEAD; only one in four patients survive 10 years (41).

How is the diagnosis of CAD made in patients with LEAD without any cardiac symptoms at all?

As mentioned in Chapter 1, a detailed investigative history and meticulous physical examination should be performed on every patient. The resting electrocardiogram (ECG) should be examined carefully, and the ABI of each patient over 50 years of age should be assessed. After LEAD is established, carotid ultrasonography should be performed in order to detect carotid plaques, flow limiting or not and the intima/media thickness (52).

Electron beam computed tomography (EBCT) (53) or ultrafast computed tomography (CT) (54) is a simple, quick, noninvasive, and inexpensive test compared to other cardiac tests and diagnostic methods. EBCT (53) is a newcomer to our diagnostic armamentarium that can indirectly assess coronary endothelial dysfunction, and, of course, coronary calcium deposits. EBCT (53) can detect calcium deposits in the coronary arterial wall. The coronary diagram based on EBCT can be used to motivate patients to modify their modifiable risk factors (Table 1). Coronary calcium deposits mean that their coronary problem has started. If the coronary calcium score is high, the lumen of the coronary arterial tree (luminogram) should be made known by performing coronary angiography. A very high calcium score is highly predictive of coronary events (55). Coronary angiography (luminography) is not the *sine qua non* method to diagnose ischemic heart disease.

The most popular method to diagnose myocardial ischemia is a myocardial perfusion scan utilizing single photon emission computed tomography (SPECT) (56,57). Myocardial perfusion can be assessed (if

the patient can walk fast) using the standard or modified Bruce (58) treadmill exercise protocol or the asymptomatic cardiac ischemia pilot (ACIP) (59) protocol combined with the IV injection of one or two radionuclide substances like Thallium-201 (^{201}Tl) and/or Technetium 99m ($^{99\text{m}}\text{Tc}$) analogs. Tomographic images of the myocardium based on perfusion are obtained at rest and following exercise. With progressive exercise, the depth of the ST segment depression on the exercise ECG (58–60) may increase involving more ECG leads, and the patient may develop angina. Stress-induced ST elevation indicates impending acute coronary syndrome and should be considered a cardiac emergency (61). Rarely, exercise-induced coronary spasm can cause ST elevation (62). Ischemic ST segment displacement may be seen not only during the exercise phase. In about 10% of patients, the ischemic response may appear only in the recovery phase; the prevalence of ischemic ST segment change in the recovery phase only, is higher in asymptomatic patients compared with the symptomatic CAD ones (63,64).

Dual isotope IV injection: both ^{201}Tl and a $^{99\text{m}}\text{Tc}$ analog are preferable to administering ^{201}Tl alone (65); myocardial perfusion can be assessed more accurately, particularly in overweight individuals, but also left ventricular function: contractility, ejection fraction objectively, as the ratio of end-systolic radioactivity counts over the end-diastolic counts. Chamber size, post stress dilatation of the left ventricle, and many times right ventricular hypertrophy or infarct can be seen on SPECT images (66). Soft tissue attenuation of the SPECT images, particularly as a result of large breasts, not necessarily gynecomastia, is a problem. Hence, breast markers are advisable. ^{201}Tl , a potassium analog, became available 30 years ago (65). In the early 1990s, new $^{99\text{m}}\text{Tc}$ labeled compounds with better imaging characteristics and novel biological properties (67) were introduced for visualization of myocardial perfusion. Perfusion images are acquired with electrocardiographically synchronized gating. Thus, accurate information is obtained for both perfusion and function. A defect present on the stress images and not present or present to a lesser degree on the rest images, i.e., a reversible defect indicates ischemia (68).

A persistent defect, that is unchanged and is present on both exercise and rest images indicates MI or scar tissue. Persistent defect or defects can also be caused by chronic severe ischemia (hibernating myocardium). In order to differentiate between severely ischemic, but still viable myocardium, from scar tissue, myocardial viability studies are indicated.

Unfortunately, a number of patients with LEAD and claudication cannot walk fast on the treadmill; they can even get claudication on the stationary bicycle. Hence, pharmacological vasodilatation with adenos-

ine or dipyridamole IV (69–71) or pharmacological stress with dobutamine provides useful alternative approaches.

There is an over 30-year experience with dipyridamole (persantine IV). Dipyridamole is infused over a 4-minute period (0.142 mg/kg/minute) (72) using an infusion pump or by slow hand injection. Approximately 4 minutes after the completion of the infusion there is maximal coronary vasodilatory effect and the isotope is injected IV immediately thereafter. Dipyridamole can dilate the normal or nearly normal coronary arterial segments, but cannot dilate to the same degree the diseased atherosclerotic coronary branches. In essence, dipyridamole creates a steal phenomenon. Blood flow follows the hemodynamic law of least resistance preferentially; there is significantly more coronary blood flow through the normal (nonatherosclerotic) dilatable segments compared to the atherosclerotic coronary segments. The decreased blood supply as detected by decreased thallium uptake (radiopenic myocardial segment) is called a perfusion defect or defects, depending on the number of left ventricular regions that are ischemic. In true ischemia, during the rest period the SPECT images show homogeneous uptake. A reversible defect or defects during stress indicates decreased uptake of the flow tracer, because there is relatively less blood flow in these segments compared to other areas. A reversible defect is diagnostic of myocardial ischemia (73–75). If the defect on the myocardial images persists even after the rest period, then this defect is called persistent defect. Persistent defect usually indicates scar tissue. MI is the commonest cause of persistent defect. Less commonly, cardiomyopathy, dilative or ischemic presents as persistent defects. As mentioned previously, a persistent defect can also be caused by chronic severe ischemia, (hibernating myocardium). In order to differentiate between severely ischemic but still viable myocardium from scar tissue, viability studies are indicated, preferably with positron emission tomography (PET) (76,77).

Intravenous infusion of dipyridamole blocks the cellular re-absorption of adenosine and, in turn, increases the concentration of adenosine, an endogenous vasodilator that can activate specific receptors (72). Coronary blood flow is autoregulated by adenosine to meet myocardial metabolic demands (72). In patients without CAD, dipyridamole or adenosine infusion creates vasodilatation and increases coronary blood flow three to five times above baseline levels. In patients with coronary disease the resistance vessels distal to the stenotic area are already dilated, often maximally, to maintain normal coronary flow at rest. In these patients (coronary patients) dipyridamole IV or adenosine IV (78) does not (cannot) cause further vasodilatation in the atherosclerotic vascular

bed or beds. Elsewhere in the myocardium, supplied by normal coronary arteries, a substantial increase in myocardial blood flow occurs. Myocardial segments supplied by atherosclerotic arteries are relatively hypoperfused compared to regions supplied by normal arteries. Pharmacological vasodilatation by adenosine or dipyridamole does not precipitate myocardial ischemia *per se*. The patient should be instructed not to have xanthine derivatives or caffeine-containing beverages or chocolate the night before, and in general substances that can block adenosine receptors, in order to avoid false-negative images (79).

Adenosine IV (maximum of 140/ μ g/kg/min) has been increasingly utilized as a pharmacological vasodilating agent in patients unable to walk fast as in LEAD (78). Persantine IV works as a vasodilating agent via endogenous adenosine. Adenosine IV can cause chest discomfort, headache, dizziness, or bronchospasm. However, in many cases, the side effect profile of adenosine is similar to a small quantity of saline IV, i.e., no side effects. The great advantage of adenosine is that it is a very short acting agent, so the side effects dissipate spontaneously and quickly. The half-life of adenosine is only 30 seconds. Transient atrio-ventricular (A-V) block, first degree, second degree, or high degree of A-V block and profound sinus bradycardia are common, but transient. The expected pharmacologic effect of adenosine is transient bradycardia and transient hypotension. In severely ischemic coronary patients, mild tachycardia or even systolic blood pressure elevation has been observed. Probably the most significant side effect of adenosine is bronchospasm; if persistent and severe, the effect of adenosine can be reversed by aminophylline IV. Of course, if the patient suffers from bronchial asthma in addition to LEAD, then adenosine should not be used. In asthmatic patients and for those who take xanthine derivatives the choice of pharmacologic stressor is dobutamine.

Dobutamine is a pharmacologic stressor that can be used in patients with LEAD. Dobutamine acts by increasing the workload of the left ventricle in three ways: (1) by increasing the heart rate, (2) by increasing the systolic blood pressure, and (3) by increasing myocardial contractility. Hence, dobutamine increases myocardial oxygen demands. Coronary blood flow increases significantly to a degree comparable to that during physical exercise (twofold to threefold), but less than that with adenosine or dipyridamole. The increase in heart rate is lower than that with exercise. Dobutamine pharmacologic stress testing is not the first diagnostic option to assess patients with LEAD for CAD. Dobutamine should not be used in patients with atrial fibrillation, because it can increase the ventricular rate excessively. Any significant side effect of

dobutamine IV, either serious sinus tachycardia or other tachyarrhythmias, or severe elevation of the blood pressure should be promptly treated with a short acting β -blocker.

DOBUTAMINE STRESS ECHOCARDIOGRAPHY

The resting transthoracic echocardiogram is compared very carefully, segment by segment with the echocardiogram during dobutamine infusion and during the recovery phase. The left ventricular contractility is analyzed in all segments and areas of hypokinesis, dyskinesis, or akinesis are studied and compared to the baseline echocardiogram.

As mentioned previously, in LEAD if the patient cannot exercise adequately myocardial perfusion imaging is done, utilizing one and preferably two radionuclide substances and a pharmacologic stressor. Commonly used pharmacological stressors are adenosine or dipyridamole IV, and if there is a contraindication to either of these two agents, such as in patients with history of bronchospasm or patients receiving xanthine containing products, then the choice should be dobutamine. In most LEAD patients who cannot walk fast the approach of choice is pharmacological stress testing with a vasodilating agent.

Stress echocardiography has high sensitivity and specificity to diagnose accurately myocardial ischemia if left ventricular hypertrophy is not present. The Treadmill protocol (44) is also utilized. In patients who cannot walk on the treadmill adequately or perform on a bicycle ergometer because of limiting claudication or other medical problems, pharmacological stress 2-dimensional echocardiogram is recommended utilizing dobutamine. Stress echocardiography is more sensitive and specific for detecting inducible ischemia than the exercise electrocardiogram (ECG) alone (80,81), even in patients who can walk incrementally faster, something patients with LEAD cannot do. The resting echocardiogram is done first, analyzing carefully the wall motion of all left ventricular segments along with the endsystolic and end-diastolic volumes, dimensions, and hemodynamics. Then the infusion of the pharmacological stressor, dobutamine begins. The patient, his or her symptoms, the BP response, the heart rate, rhythm, the regional wall motion, the ventricular volume changes, and the ST changes are observed carefully and diligently. The additional IV injection of a perfluoro carbon-based contrast agent or sonicated albumin (trade name optison) can give beautiful images of myocardial perfusion and impressive details. Dobutamine stress ECG with a contrast medium is an excellent method to study a patient with LEAD for ischemic heart disease with three preconditions: (1) there is no atrial fibrillation because dobutamine can increase the

ventricular rate excessively; (2) there is no left ventricular hypertrophy (LVH), so that wall motion analysis can be performed accurately; and (3) the resting BP is not significantly elevated. The transthoracic echocardiogram obtained at rest is compared with the one obtained during pharmacologic stress testing with IV dobutamine and in the post-stress period. Dobutamine or exercise echocardiogram combined with a contrast agent IV infusion is an excellent noninvasive diagnostic method to assess cardiac function. The contrast medium follows the coronary blood flow. An accurate diagnosis of myocardial ischemia, MI, or normally perfused myocardium can be made. Two-dimensional echocardiography can also provide clinically useful information on cardiac chamber size, cardiac volumes, intracardiac pressures, and valve function. Information about the thoracic aorta can also be obtained.

In patients who have risk factors for LEAD and CAD in whom no LEAD and no demonstrable carotid disease or myocardial ischemia can be diagnosed, utilizing noninvasive techniques, a regular cardiovascular evaluation should be done once or twice a year, because of the high probability of developing cardiovascular disease as time goes on.

The accurate assessment of myocardial ischemia is useful, not only to establish the diagnosis of ischemic heart disease and prescribe anti-ischemic therapy: a β -blocker (even in the presence of LEAD), a statin to keep the LDL very low (statin therapy also reduces CRP levels), an antiplatelet agent such as 75 mg of clopidogrel every day or 325 mg per day of enteric coated aspirin. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) have been introduced in our pharmacotherapeutic panoply of LEAD and CAD in order to improve endothelial function and left ventricular performance. In diabetic patients in particular, ARBs have been shown to slow the progression of diabetic microvasculopathy and protect them to some degree from diabetic nephropathy. Diabetic patients even in the absence of demonstrable LEAD and CAD have coronary endothelial dysfunction, and secondary prevention with a statin and an antiplatelet agent should be recommended.

Whenever the medical history, detailed physical examination, and the resting ECG were used, between 20 and 50% of patients with symptomatic LEAD were found to have evidence of CAD (82). When myocardial perfusion studies or coronary angiography are applied, CAD was diagnosed in 60 to 90% of patients with LEAD. Indeed, many patients with LEAD also have CAD. The prevalence of cerebrovascular disease in patients with LEAD is also significant; again a detailed history and a meticulous physical examination alone resulted in prevalence values for

cerebrovascular disease ranging from 0.5 to 15% in patients with LEAD (33). In order to detect cerebrovascular disease co-existing with LEAD, the clinician should use sensitive and specific noninvasive tests. The most widely used method is Doppler ultrasonography of the cranial arteries. Carotid ultrasound studies in patients with LEAD show an exponential increase of the risk for cardiovascular events when carotid stenosis exceeds 50% of the lumen, even after successful PCI (51,83).

MANAGEMENT

The cornerstone of medical therapy in any type of cardiovascular disease, LEAD, carotid artery disease, and CHD is aggressive risk factor modification. The goal for systolic pressure is 120 mmHg in the arm, which shows the highest pressure. The goal for diastolic pressure should be less than 90 mmHg according to the most recent guidelines of the Joint National Committee (JNC7) on Hypertension (84).

In patients older than 50 years of age, a systolic pressure of greater than 130 mmHg is more of a serious risk factor for atherosclerosis than a mildly elevated diastolic pressure is. In patients 50 years or younger both systolic and diastolic pressure elevations can be damaging.

The blood sugar ideally should be controlled with regular checks of the fasting blood glucose level and of hemoglobin A1C (6). Hyperglycemia should be controlled by a diet low in carbohydrates and low in animal fat. Regular exercise such as brisk walking, use of treadmill or stationary bicycle for an average of 45 minutes a day or swimming should become routine for every cardiovascular patient. The pharmacotherapeutic armamentarium for diabetes mellitus keeps expanding. Pharmacologic agents, which can potentially improve endothelial function and tone are preferable.

EXTRA-LOW LDL CHOLESTEROL

Improvement of the lipid profile is beneficial to all vascular patients with or without demonstrable coronary disease. The goal for the LDL-C is well below 90 mg/dL or as low as possible, a natural occurrence in parts of China and Japan. The recommendation for an LDL well below 90 mg/dL stems from many clinical trials utilizing statins. The prevailing trend today based on recently completed large clinical trials is extra-low LDL-C; a median level of 78.9 mg/dL (85) and 62 mg/dL (86). Patients with extra-low cholesterol levels had prospectively fewer cardiac deaths and fewer overall cardiovascular events. The optimally lowest level of LDL-C is unknown. Analysis of the ARBITER study (87) shows a greater likelihood of regression of atherosclerosis across a broad

range of LDL-C values with the greatest likelihood of regression at a LDL-C below 70 mg/dL. Regression of atherosclerosis demonstrated by intra vascular ultra sonography (IVUS) imaging in the coronary circulation or in LEAD is an established surrogate for clinical benefit—LDL-C reduction should go well below the current National Cholesterol Education Program (NCEP) (88) value of 100 mg/dL. Regression of carotid atherosclerosis demonstrated by carotid B-mode ultrasound is directly related to the absolute LDL-C level on statin therapy. The greatest regression was obtained with an LDL-C below 70 mg/dL (89).

The axiom should be for all vasculopathic patients with regards to LDL-C: the lower the better.

The goal for HDL-C should be more than 40 mg/dL for men and more than 50 mg/dL for women (8,90). Hypertriglyceridemia, which has been strongly associated with LEAD (4), should be aggressively treated with weight reduction, exercise, and a high protein, high fiber diet. High protein, high fiber diets, both short term and long term, reduce body weight significantly, reduce triglycerides, and hence improve endothelial function. Elevated triglycerides can induce endothelial cell dysfunction and serve as a marker for increased serum concentrations of lipoprotein remnant particles, which are highly atherogenic (13,91–93).

Pharmacotherapeutically, a short-acting statin such as simvastatin 20 mg as a starting dose after dinner and fenofibrate 160 mg (92,94) with breakfast has been proven safe and effective for the reduction of triglyceride blood levels and LDL-C. The two pharmacologic agents should be given about 10–12 hours apart to avoid overlap of their half lives and potential liver toxicity. Fibrates should not be co-administered with long-acting statins; the possibility of hepatotoxicity and rhabdomyolysis is real, particularly after a fall resulting into muscle trauma and/or unexpected renal dysfunction.

The Heart Protection Study (95) included 20,536 persons aged 40–80 years with a serum total cholesterol of 135 mg/dL or higher and prior MI (8510 persons), other CAD (4876 persons), or no CAD (7150 persons) (95). Of the 7150 persons without CAD, 1820 had cerebrovascular disease, 2701 had LEAD, and 3982 had diabetes mellitus. Although treated hypertension was present in 8457 persons, only 237 persons were included on the basis of hypertension alone. Patients were randomized to simvastatin 40 mg daily or to placebo. Mean follow-up was 5 years.

Compared to placebo, simvastatin caused significant reduction in all-cause mortality by 13%, in any vascular death by 17%, in major coronary events by 27%, in any stroke by 25%, in coronary or noncoronary revascularization by 24%, and in any major vascular event by 24% (95). In the 3500 persons with an initial serum LDL-C of <100 mg/dL,

reduction of the serum LDL-C level from 97 mg/dL to 65 mg/dL by simvastatin caused a similar reduction in risk as did treatment of patients with higher serum LDL-C levels (95). Simvastatin significantly reduced all-cause mortality, vascular death, major coronary events, coronary or noncoronary revascularization, and any major vascular event regardless of initial levels of serum lipids, age, or gender (95). On the basis of these data, the Heart Protection Study investigators recommended treating patients at high risk for vascular events with statins, regardless of the initial levels of serum lipids, age, or sex (95).

In the reversal of atherosclerosis with aggressive lipid lowering (REVERSAL) study, intravascular ultrasound was used to measure progression of atherosclerosis in 502 patients with CAD randomized to pravastatin 40 mg daily or atorvastatin 80 mg daily (85). The serum LDL-C level was reduced to 110 mg/dL in the pravastatin group and to 79 mg/dL in the atorvastatin group. At 18-month follow-up, compared with baseline values, patients treated with atorvastatin had no change in atheroma burden, whereas patients treated with pravastatin showed progression of coronary atherosclerosis (85).

At 3-year follow-up of 1410 persons, mean age 81 years, with prior MI and a serum LDL-C level of 125 mg/dL or higher, reducing the serum LDL-C level by statins to <90 mg/dL was associated with a 20% incidence of new coronary events, whereas reducing the serum LDL-C level to 90–99 mg/dL was associated with a 48% incidence of new coronary events (96). In this study, the incidence of new stroke was 7% if the serum LDL-C level was reduced to <90 mg/dL and 16% if the serum LDL-C was reduced to 90–99 mg/dL (94).

In 4162 patients hospitalized for an acute coronary syndrome, the median serum LDL-C level was 95 mg/dL in patients randomized to pravastatin 40 mg daily vs 62 mg/dL in patients randomized to atorvastatin 80 mg daily (86). At 2-year follow-up, the primary endpoint of death from any cause, MI, documented unstable angina pectoris requiring rehospitalization, coronary revascularization (performed at least 30 days after randomization), and stroke was 26.3% in the pravastatin group vs 22.4% in the atorvastatin group, a 16% reduction in favor of atorvastatin ($p = 0.005$) (86).

The LDL-C should be kept well below 90 mg/dL, actually closer to 50 mg/dL, utilizing a low cholesterol, low animal fat diet, exercise, and a powerful statin (97). Statins have pleiotropic effects: plaque stabilization, vasodilatation, anti-inflammatory, antithrombotic, antiproliferative, and antioxidant (98). Most statins are metabolized via the CYP 3A4 pathway. Hence, drugs which also use the CYP 3A4 metabolic pathway, like ketoconazole, nefazodone, cyclosporine, nifedipine, felodipine,

nisoldipine, macrolide antibiotics, and erythromycin in particular should not be used with most statins concomitantly. Sadly, many case reports have described the development of rhabdomyolysis when lovastatin was combined with erythromycin (99). Erythromycin alone can cause QT prolongation (100). If macrolide antibiotics are necessary, then the CYP 3A4 statin should be discontinued for the duration of the antibiotic therapy.

Intensive statin therapy bears benefits both short term and long term; it reduces the probability for cardiovascular events. Statin therapy also improves time to claudication.

In a recent study (101), simvastatin 40 mg significantly increased treadmill exercise time to onset of claudication from baseline by 54 seconds (a 24% increase $p < 0.0005$) at 6 months after treatment and by 95 seconds (a 42% increase, $p < 0.0001$) at 1 year of treatment. At 6 months and 1 year after treatment with placebo, treadmill exercise time until onset of intermittent claudication was not significantly different from baseline exercise time (101,102).

WHAT IS THE SIGNIFICANCE OF LOW HDL CHOLESTEROL?

Low serum HDL-C predisposes patients to the development of MI (90), sudden death (103), stroke (104,105), carotid artery disease (106), restenosis after angioplasty (107), multivessel disease, and atheromatous plaque formation in the proximal left main coronary artery (108), and disability and loss of ability to execute activities of daily living in the elderly (109). Low levels of HDL are highly prevalent and occur in approximately 35% of men and 15% of women (24).

Conversely, high HDL-C is correlated with longevity and protection from atherosclerotic disease and cognitive impairment (25). In the Framingham risk equation, an HDL >60 mg/dL is defined as a negative risk factor, and was given the numerical designation of -1 . An early meta-analysis of data from the Framingham Study, the Multiple Risk Factor Intervention Trial, the Lipid Research Clinics Coronary Primary Prevention Trial, and the Lipid Research Clinics Prevalence Mortality Follow-up Study revealed that for every 1 mg/dL rise in serum HDL-C, risk of CAD in men and women decreased approximately 2% and 3%, respectively (110). The most important antiatherogenic function of HDL-C is likely its ability to drive the reverse cholesterol transport (RCT) (111). RCT consists of a series of reactions by which HDL is able to induce the net delivery of systemic cholesterol back to the liver for disposal as bile salts or to steroidogenic organs (e.g., adrenals, ovaries,

testes) for conversion to steroid hormones. As long as RCT is able to outpace the accumulation of cholesterol in the vascular wall, the progression of atherosclerotic disease is prevented. The net effect of RCT (increased bile salt formation) has been verified in clinical studies (111). It is postulated that increased RCT provides the basis for the intravenous infusion of HDL or bioengineered HDL in order to induce regression of the atheromas in clinical trials (112). HDL is able to reduce the oxidation of LDL via the activity of two of its constituent enzymes, paraoxonase (113) and platelet activating factor acetylhydrolase (114), thus rendering it less atherogenic. HDL inhibits endothelial cell apoptosis (115) and stimulates endothelial cell proliferation along denuded areas of the vessel wall (116). HDL is able to reverse endothelial cell dysfunction by stimulating endothelial nitric oxide synthetase activity (117). As HDL levels increase, the capacity for arterial vasodilation increases. High HDL decreases endothelial cell adhesion molecule (vascular cell adhesion molecule [VCAM]-1), and intercellular adhesion molecule (ICAM)-1 expression (118,119), thus the capacity for leukocyte infiltration and progression of inflammation within the vascular walls decreases (117). HDL is antithrombotic by virtue of its ability to decrease platelet aggregability (120), stimulate prostacyclin production (121), and potentiate the activity of proteins C and S (122).

As mentioned earlier, decreased HDL-C levels constitute a major risk factor for CAD and LEAD. A novel therapeutic approach to raise HDL is inhibition of cholesteryl ester transfer protein (CETP) (123). Individuals with CETP deficiency as a result of molecular defects in the CETP gene, have markedly elevated plasma levels of HDL-C and apolipoprotein A-I (124).

Torcetrapib, a potent inhibitor of CETP, markedly increases HDL-C levels and also decreases LDL-C levels, both when administered as monotherapy and when combined with a statin (123).

Elevated triglycerides have also emerged as an independent risk factor for the development of coronary atherosclerotic disease (125) and LEAD in particular. The Prospective Munster Cardiovascular Study (126) showed that elevations in serum triglyceride levels increased risk for CAD independent of serum LDL-C and HDL-C. In the Copenhagen Male Study (127) there was a clear gradient of increasing risk for CAD as serum triglyceride levels rose. A meta-analysis of 17 trials supports the conclusions that hypertriglyceridemia is an independent risk factor for CAD, and the risk rises progressively as the severity of hypertriglyceridemia increases (128). Elevated triglycerides can cause endothelial dysfunction (129) and serve as a marker for increased serum concentrations of lipoprotein remnant particles. Remnant particles are

incompletely catabolized very low density lipoprotein (VLDL) and chylomicra and are highly atherogenic (129).

The combination of high triglycerides and low HDL-C significantly increases the risk for CAD and LEAD, and is a frequent finding in patients with insulin resistance (130). Hyperinsulinemia induces a dysregulation of adipose tissue metabolism (130). Adipocyte triglyceride catabolism increases, causing a flux of free fatty acids into the liver. The liver in turn increases VLDL secretion. Hyperinsulinemia is also associated with decreased lipoprotein lipase activity and increased hepatic lipase activity (130). As lipoprotein lipase activity decreases, the hydrolysis of triglycerides in VLDL and chylomicra decreases. This results in hypertriglyceridemia and increased remnant particle formation. HDL-C levels drop in patients with insulin resistance (130,131). The American Diabetes Association has defined optimal HDL-C and triglycerides in patients with type 2 diabetes mellitus at least 40 mg/dL and less than 150 mg/dL, respectively (132). Based on multivariate analysis of risk factors from the United Kingdom Prospective Diabetes Study (133), the two most important risk factors to modulate for decreasing CAD risk are the reduction of LDL-cholesterol and the elevation of HDL.

Fibrates increase serum HDL-C levels by stimulating the hepatic expression of apoprotein A-I and A-II (Apo A-I, Apo A-II) (134,135). These apoproteins help to drive the formation of HDLs. Multiple studies have demonstrated a clear reduction in risk for CAD as serum levels of Apo A-I increase (136,136). Fibrates may also increase rates of RCT by increasing the expression of ABCA1 in macrophages (138). Fibrates stimulate triglyceride metabolism via a number of pathways.

Inflammation plays a key role in the etiology of atherosclerosis (139). A plethora of interleukins, cytokines, intercellular matrix modifying enzymes, and cell types interact to promote foam cell, fatty streak, and atheromatous plaque formation (140). PPAR- α has emerged as an important mediator of vascular inflammation and cellular redox status (141). The nuclear factor κ B (NF- κ B) pathway regulates the expression adhesion molecules, interleukin-6, cyclooxygenase-2, and endothelin-1 (141). CRP is an important modulator of and marker for atherosclerotic disease (142,143). PPAR- α agonism with fibrate therapy decreases serum CRP levels (94,144).

Fibric acid derivatives have been used in a variety of clinical trials in an effort to demonstrate their efficacy in reducing both cardiovascular morbidity and mortality and the progression of atherosclerotic disease. These trials also demonstrate the importance of increasing serum HDL and reducing triglycerides when attempting to decrease risk for acute

cardiovascular and cerebrovascular events in both primary and secondary prevention trials. In the Veterans Affairs High-Density Lipoprotein Intervention Trial (VAHIT) (145), men with CAD and mean LDL 111 mg/dL, mean HDL 31 mg/dL, and mean triglyceride 161 mg/dL were treated with either gemfibrozil (600 mg po bid) or placebo over a five-year follow-up period. The treatment group experienced a 6% elevation in HDL, no change in LDL, and a 31% decrease in triglycerides (145). Among patients in the treatment group, gemfibrozil therapy resulted in a 22% ($p = 0.006$) reduction in the composite endpoint of all-cause mortality and nonfatal MI. Treatment with gemfibrozil reduced the risk of stroke and transient ischemic attacks by 31% ($p = 0.36$) and 59% ($p < 0.001$), respectively, and decreased the need for carotid endarterectomy by 65% ($p < 0.001$) (145). A trend for reducing cerebrovascular event rates with gemfibrozil therapy was apparent within 6–12 months. The diabetic patients enrolled in VAHIT benefited the most from gemfibrozil therapy, with reductions of 32% ($p = 0.004$) in the combined endpoint, 41% ($p = 0.02$) in cardiac death, and 40% in stroke ($p = 0.046$) (145). Among patients with hyperinsulinemia, the benefit of gemfibrozil therapy increased as the severity of insulin resistance rose (145). Of considerable importance is the fact that VA-HIT was the first trial to show a reduction in cardiovascular and cerebrovascular events with an antilipemic medication independent of changes in serum LDL. Most of the benefit of fibrate therapy in this trial was attributed to HDL elevation and the pleiotropic effects of gemfibrozil (145).

Multiple angiographic trials with fibrates have demonstrated the ability of these drugs to reduce rates of atheromatous plaque progression. The Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT) (146) compared bezafibrate 200 mg po tid to placebo in 92 men who suffered a MI at age <45 years (146). The study patients underwent coronary angiography at time of entry into the trial and then after 2 or 5 years of therapy. The mean minimum luminal diameter decreased over the follow-up period by 0.06 mm and 0.17 mm in the bezafibrate and placebo groups, respectively. The change in rate of disease progression was statistically significant ($p < 0.049$) and was achieved with a 31% reduction in triglycerides, 9% elevation in HDL, and no change LDL (146). In the Lopid Coronary Angiography Trial (LOCAT) (147), 395 men who had undergone revascularization with CABG were randomized to either gemfibrozil (600 mg po bid) or placebo. Patients underwent coronary angiography at time of study entry and then after 32 months of therapy (147). Gemfibrozil therapy significantly reduced rates of plaque progression in coronary vessels and the development of new

plaques in saphenous vein grafts. Gemfibrozil caused reduction in stroke rate in men with CAD and low HDL (148). The benefit in LOCAT was attributed to a 9% elevation in HDL and a 33% reduction in remnant lipoprotein particle formation (147).

Patients with hypertriglyceridemia may have low LDL levels. However, fibrate therapy stimulates the conversion of VLDL to LDL; triglyceride levels drop, but LDL can rise, sometimes substantially. In this situation, the addition of a short-acting statin such as simvastatin after dinner or a cholesterol absorption inhibitor such as ezetimibe (Zetia) (149), may become necessary. In general, the combination of statins with gemfibrozil should be avoided. Gemfibrozil can inhibit the glucuronidation of statins, thereby reducing elimination of the statin thus raising the risk for hepatotoxicity and skeletal muscle toxicity, including rhabdomyolysis (150–153). Fenofibrate is a much safer alternative because it does not adversely impact the metabolism of rosuvastatin (154) or pravastatin (155). Moreover, unlike gemfibrozil, fenofibrate can provide additional capacity for further reducing serum LDL levels. Fenofibrate (Tricor) decreases the expression of a variety of inflammatory mediators (CRP, interleukin 1- β , soluble CD40, and soluble CD40-ligand) and substantially improves forearm flow-mediated dilatation of the brachial artery (a surrogate of coronary endothelial function) when combined with simvastatin to treat patients with mixed hyperlipidemia (94).

In dislipemic coronary patients with claudication, combination therapy with simvastatin 40 mg and ezetimibe (149) 10 mg (trade name of the combination preparation Vytorin) after dinner combined with fenofibrate (Tricor) 160 mg (94) with breakfast brings a significant improvement in walking time to onset of claudication, and time to absolute claudication (*see* Chapter 1) measured on the treadmill (personal observations). There is also a remarkable improvement of the patient's lipid profile with this combination therapy.

A combination therapy of rosuvastatin (Crestor) (156) and fenofibrate (Tricor) (154) has been gaining popularity among vascular physicians and cardiologists. Rosuvastatin can keep LDL very low and can also increase the plasma levels of HDL (97,156). Fenofibrate (94) in the morning can bring a remarkable reduction of the serum triglycerides. Rosuvastatin and fenofibrate is a safe combination therapy with regards to liver toxicity and rhabdomyolysis (154,156).

EFFECTS OF NIACIN

Niacin positively impacts lipoprotein metabolism through multiple mechanisms. Niacin appears to block HDL particle uptake and catabo-

lism by the liver cells without adversely affecting cholesteryl ester delivery to the liver (157). Unlike statins and fibrates, niacin does not stimulate hepatic biosynthesis of HDL. Niacin has also been shown to reduce Lp(a) biosynthesis. Lp(a) is procoagulatory and is a highly atherogenic variant of LDL. Small dense LDL is believed to be more atherogenic than its large buoyant form because it has a higher susceptibility to oxidation, has a lower affinity for the LDL receptor on hepatocytes, and has increased access to the arterial wall subendothelial space by virtue of its smaller physical volume. Niacin has been shown to alter the distribution of LDL particle sizes by increasing the concentration of large buoyant LDL and decreasing the concentration of small, dense and highly small LDL particles (158). Extended release niacin is safe (159) and beneficial to all components of the lipid profile (160).

Niacin can induce significant skin flushing secondary to prostaglandin-mediated dermal vasodilation. Aspirin and other salicylates are potent inhibitors of cyclooxygenase and prostaglandin biosynthesis. Hence, salicylates can be used to prevent facial flushing, i.e., aspirin 325 mg concomitantly with long acting niacin. Niacin can cause gastric irritation, nausea, bloating, pruritus, and acanthosis nigricans (161). Slo-Niacin was developed to slow the rate of absorption of niacin and decrease the risk of flushing. Both crystalline niacin and Slo-Niacin are associated with significant risk for hepatotoxicity, especially when used at doses that exceed 2 g/day (161,162).

Niacin therapy can induce mild elevations in glucose levels. For this reason, many clinicians have been hesitant to use niacin therapy in patients with diabetes mellitus or impaired glucose tolerance (IGT) out of concern that it would significantly antagonize glycemic control (161). The Assessment of Diabetes Control and Evaluation of the Efficacy of Niaspan (ADVENT) trial evaluated the effect of two doses of Niaspan vs placebo on glycemic control in 148 patients with LEAD and type 2 diabetes mellitus during 4 months of follow-up (161). Glycosylated hemoglobin values at baseline and after 4 months of therapy were: placebo, 7.13% and 7.11%; Niaspan 1000 mg daily, 7.28% and 7.35% ($p = 0.16$ vs placebo); Niaspan 1500 mg daily, 7.2% and 7.5% ($p = 0.48$ vs placebo). In diabetic patients such small changes in overall glycemic intolerance control can be offset by titrating insulin or antiglycemic medication as indicated (163). Among patients with carbohydrate intolerance (fasting blood sugar 110–125 mg/dL), high-dose niacin therapy can disturb glycemic control enough to meet criteria for diabetes mellitus (fasting blood sugar >126 mg/dL). Consequently, patients with established glucose intolerance should be monitored closely for increases

in serum glucose when placed on niacin therapy (161,164). When evaluated over one year of follow-up, the Arterial Disease Multiple Intervention Trial (ADMIT) demonstrated that niacin at doses of up to 3 g/day given to 64 patients with diabetes mellitus had no effect on glycosylated hemoglobin levels (7.8% at baseline and after 48 weeks of therapy) (163). Serum glucose levels were minimally increased in diabetics and nondiabetics by 8.7 and 6.3 mg/dL, respectively (163,165).

Extended-release niacin (Niaspan: dosing range 375–2000 mg daily) used as monotherapy at a dose of 2000 mg daily decreases LDL by 17%, triglycerides by 35%, and Lp(a) by 24%, and increases HDL by 26% (166). These alterations in lipoprotein values are stable more than 2 years of follow-up (166). The rationale behind the bedtime administration of Niaspan is based on two important clinical issues. The first is that if flushing does occur the patient may simply sleep through it. The second has to do with the finding that during the nighttime fast the rate of adipose tissue lipolysis increases and serum triglycerides surge to their highest level at any point in a 24-hour cycle (167). Niacin has been shown to inhibit this overnight surge in serum triglycerides (167). This may have important additional consequences because postprandial hypertriglyceridemia is associated with significant endothelial dysfunction. Combination therapy of niacin and colestipol has beneficial effects on coronary atherosclerosis and coronary venous bypass grafts (168,169).

In the Coronary Drug Project (170), niacin therapy compared to placebo reduced the combined endpoint of nonfatal MI and CHD death by 14% ($p < 0.05$), nonfatal MI by 27% ($p < 0.005$), stroke and transient ischemic attack by 26% ($p < 0.05$), and the need for CABG by 67% ($p < 0.005$) during the 5-year follow-up period. After an additional 9 years of follow-up subsequent to completion of the study, all-cause mortality was 11% lower ($p < 0.001$) in the niacin-treated group compared to those patients given placebo (171).

The HDL-C should exceed 50 mg/dL, preferably with exercise and vitamin B3, i.e., long-acting niacin (166,167) at a starting dose of 500 mg and gradual increments of the dose to 1 g or more, once a day after dinner and aspirin 325 g to ameliorate or abort facial vasodilatation as already described earlier. Aspirin decreases the cutaneous vasodilatation and hyperemia that may scare uninformed patients causing noncompliance to niacin therapy.

Long-acting niacin (167) in incremental doses at bedtime is very effective and safe in raising HDL-C. The starting dose can be 500 mg at bedtime for a week, 750 mg the second week, and 1 g or more thereafter. Long-acting niacin should be given after dinner. Improvement of the

lipid profile of vascular patients, HDL in particular, can also infer clinical benefits and vascular wall benefit, improvement of endothelial function, long term and short term. We should re-emphasize some of the key benefits of raising HDL:

- HDL inhibits endothelial cell apoptosis (115).
- Stimulates endothelial cell proliferation along denuded areas of the vascular wall (116).
- HDL reverses endothelial cell dysfunction by stimulating endothelial nitric oxide synthetase activity (117).
- Long-acting niacin is safer than short-acting niacin with regard to liver toxicity (162,166).
- Long-acting niacin should be given after dinner with enteric-coated aspirin, 325 mg, in order to prevent skin flushing caused by dermal vasodilatation. Aspirin and other salicylates are potent inhibitors of cyclooxygenase and prostaglandin biosynthesis (161). Patient compliance is very important both short term and long term.
- The most common noncompliance side effect of niacin preparations is facial vasodilatation and flushing.
- Raising HDL can inhibit the progression of atherosclerosis by enhancing reverse cholesterol transport (RCT) (110–112). RCT consists of a series of reactions by which HDL induces the net delivery of systemic cholesterol back to the liver for disposal as bile salts or to organs (adrenals, ovaries, testes) for conversion to steroid hormones (111).

Low HDL-C levels constitute a major risk factor for CAD and LEAD. A novel therapeutic approach to raise HDL is inhibition of CETP (123).

It is worth re-emphasizing the following observations: in dislipemic patients with claudication, combination therapy with simvastatin 40 mg (95) and ezetimibe (zetia) 10 mg (149) after dinner combined with fenofibrate (94) (Tricor) 160 mg with breakfast brings a significant improvement in the walking time to onset of claudication and time to absolute claudication (*see* Chapter 1) measured on the treadmill (personal observations). There is also a remarkable improvement of the patient's lipid profile with this combination therapy.

A combination therapy of rosuvastatin (97,156) (Crestor) and fenofibrate (Tricor) (94,154) has been gaining popularity among vascular physicians and cardiologists. Rosuvastatin can keep LDL very low (a key goal) and also increase the plasma levels of HDL. Fenofibrate (94) in the morning can bring a remarkable reduction of the serum triglycerides (94). Rosuvastatin and fenofibrate is a safe combination therapy with regards to liver toxicity and/or myositis (154).

Obesity should be aggressively approached with dietary programs avoiding animal fat and sugars; regular exercise; and in morbidly obese

patients, the combination of the FDA approved phentermine taken every morning with a selective serotonin reuptake inhibitor (SSRI), preferably at nighttime, because in some patients antidepressants may cause somnolence. Overtly obese patients should be frequently counseled, and symptoms and stigmata of depression should be sought. Morbidly obese patients with CAD and LEAD can be referred for one of the newer gastric interventional procedures of bariatric surgery, provided of course that myocardial ischemia if present is adequately treated preoperatively.

High serum homocystein (*22,23,172*) is an important risk factor for both LEAD and CAD. Elevated levels of homocystein have been successfully dealt with green leafy salads and other foodstuffs rich in folic acid and also with pharmacologic preparations containing folic acid and vitamin B complex.

A pharmacologically safe strategy to deal with elevated Lp(a) is to keep the LDL-C very low with a statin and heart healthy, low animal fat diet. If LDL is already low and high Lp(a) stands out as an independent risk factor, then a long-acting niacin (*162,166*) preparation can be utilized. For dislipidemic vasculopathic patients with high serum triglycerides and high LDL-C, the combination of a low dose, short-acting statin like simvastatin (*95*) at bedtime and fenofibrate (*94,154*) with breakfast or alternatively long-acting niacin can be cautiously tried. Regular blood sample analyses of liver function and of the skeletal muscles both clinically and with CPK assessment is necessary in vasculopathic patients who have high LDL-C and low HDL-C, and are placed on combination therapy with extended-release niacin 1 g at bedtime with aspirin 325 mg to prevent vasodilatation and simvastatin 20 mg or lovastatin 20 mg. The lipid profile of the patient improves remarkably. There is minimal overlap of the half-lives of extended-release niacin and simvastatin, if they are given 12 hours apart. For the forgetful patient with LEAD and CAD this author finds the combination therapy (one pill) approach of long-acting niacin with lovastatin (trade name Advicor) very gratifying, not only in improving the lipid profile but claudication as well. Sedentary patients should be aggressively motivated to participate in exercise programs, preferably as a form of group therapy for psychological and social support in tandem with antilipid therapy. Exercise therapy should be combined with pharmacotherapy and a diet rich in antioxidants like the Mediterranean diet. The Mediterranean diet improves endothelial function (*173*).

By far, the most important therapeutic intervention in any patient with LEAD and CAD is smoking cessation. Smoking is the strongest risk factor for arterial disease progression, cardiovascular morbidity, and mortality from MI, thrombotic stroke, and cardiovascular death. Smok-

ing cessation should be approached by the clinician systematically with frequent calls to the patient and to his friends and family, encouraging him to start decreasing the number of cigarets smoked per day. Many smokers, men and women, can succeed to decrease the number of cigarettes to five per day. Reduction below five cigarettes per day in the unfortunate 10% of all the smokers who develop hardcore addiction to nicotine (an addiction similar to cocaine) is extremely difficult. Smoke cessation programs do exist and should be sought out by all physicians.

A successful pharmacotherapeutic approach is cutaneous nicotine patch combined with Zyban (welbutrin) as an aid to smoking cessation treatment (174). This pharmacological combination should be continued for at least 6 months.

LEAD assessed clinically or more accurately by noninvasive testing is an adverse prognosticator in patients with CAD. LEAD increases the likelihood of cardiovascular mortality (175–177). This increased mortality of CAD, when it coexists with LEAD, is true for any type of therapeutic modality applied for CAD: medical therapy, percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG) (37,44,48–50).

The risk of death among patients with LEAD is high; only one in four patients survive 10 years (41). Co-existing CAD adversely influences the results of surgery for LEAD as the landmark study by Hertzner and coworkers (176,178,179) showed in 1000 patients, who underwent coronary angiography pre-operatively. Compared to normal subjects over a 10-year follow-up period mortality among patients with LEAD is about threefold for total mortality and about sixfold for cardiovascular and coronary disease mortality (42). In this well-executed study (42), the conclusion of a three-fold increase in all cause mortality and a sixfold increase in cardiovascular and coronary disease mortality was adjusted for age, gender, smoking, blood pressure (BP), LDL-C, HDL, triglyceride level, glycemia, and BMI.

LEAD is an independent risk factor for CAD and a prognosticator of cardiovascular mortality (87–89,180). Cardiovascular death rates are higher in men than in women. In patients with LEAD, morbidity from coronary heart disease and stroke is increased: 2.5 times more likely to present with morbidity from all forms of cardiovascular disease compared to subjects who do not have LEAD (44). There is a graded effect of the ABI on survival (45). The 10-year survival estimates among those patients with an ABI of less than 0.4 was only 33%, whereas the group with ABI ranging between 0.4–0.85 had a survival rate of 51%. Three out of four patients with an ABI greater than 0.85 survive 10 years (45).

Almost identical statistical associations were found by the frequently cited San Diego Study (48).

A detailed medical history and physical examination combined with measurement of the ABI in patients over 50 years of age is a cost effective, sensitive, and noninvasive approach, even if the individual has no clinical evidence of cardiovascular disease. Because a low ABI predicts an increased risk for cardiovascular events including death (87–89,180), the clinician should feel compelled to aggressively modify and treat all modifiable risk factors for cardiovascular disease and myocardial ischemia, no matter how silent the latter may be, if the particular patient has a low ABI. In patients with myocardial ischemia, silent or symptomatic, aggressive polypharmacy should be applied: statin therapy, beta blockade, coronary vasodilating agents like mononitrates and a long acting calcium channel blocker, antiplatelet agents, and newer agents to improve endothelial function (85,94,97,98,131,154). Aggressive polypharmacy (181) should be combined with a low or no animal fat diet and exercise therapy. Heart healthy diet, exercise therapy, and pharmacotherapy (polypharmacy is not a bad word in treating patients with LEAD and CAD) should be continued for life, in addition to PCI or peripheral vascular interventions or surgery. It should be re-emphasized that LEAD has an adverse effect on coronary patients treated with either PCI or CABG. LEAD is a strong independent and adverse predictor of long-term mortality in patients with stable CAD (87–89,180). Hence, aggressive medical therapy and global revascularization (Fig. 2) is warranted in this high-risk group of patients with LEAD and myocardial ischemia (182,183).

An increasing number of cardiac surgeons prefer to do coronary bypass surgery in patients who also have LEAD off cardiac pump on the beating heart. Perioperative complications and embolic events are fewer and the length of stay following CABG shorter. The PCI of choice should be stenting with drug-eluting stents (DES) to minimize restenosis. CABG is recommended for diabetic patients with multivessel CAD.

After revascularized procedure, pharmacotherapy and a heart healthy, low animal fat diet should be continued for life in patients with CAD and LEAD.

It should be noted that the prevalence of CAD in patients with LEAD is high; it depends on the diagnostic methodology used; if coronary arteriography is used (179) the prevalence of CAD in LEAD patients reaches 92%. However, as mentioned earlier in this chapter, screening for ischemic heart disease in patients with LEAD is done by myocardial perfusion studies: adenosine, dipyridamole, and if there is a contraindication

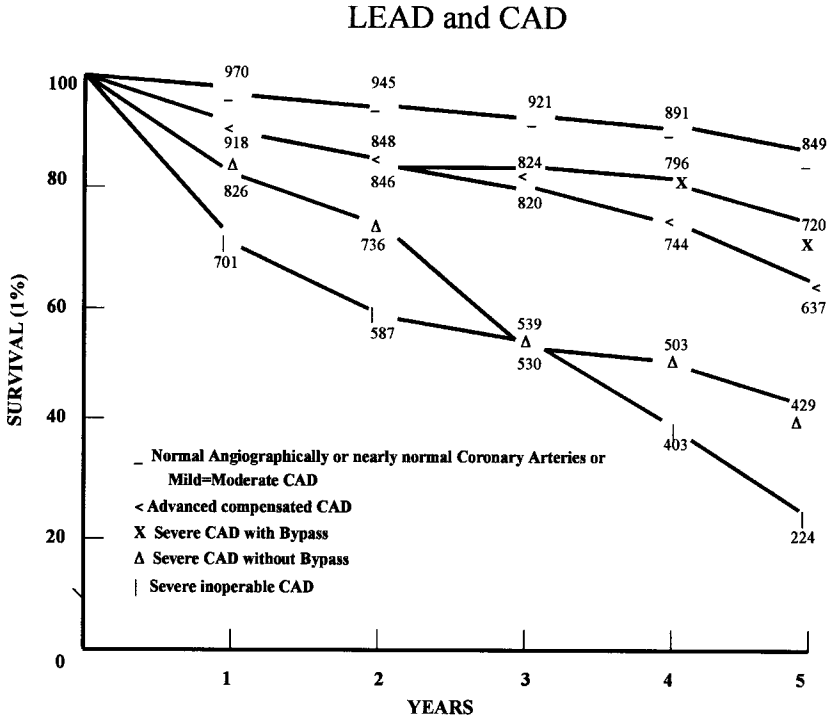


Fig. 2. The survival of patients with LEAD depends on the severity of the co-existing CAD. Adapted from refs. 178 and 179.

cation to either one of these two agents, dobutamine, dual isotope single photon emission computed tomographic images or stress ECG, preferably with contrast.

Our patients with LEAD are LEADers: and we follow.

REFERENCES

1. Hughson WG, Mann JI, Garrod RJ. Intermittent Claudication. Prevalence and risk factors. *Br Med J* 1978; 1:1379-1381.
2. Sowers JR. Obesity as a cardiovascular risk factor. *Am J Med* 2003; 115:375-41S.
3. Richard RL, Austin A, Webster IW. Predicting abstainers in smoking cessation programme administered by general practitioners. *Intl J Epidemiol* 1988; 17: 530-534.
4. Fowkes FG, Housley E, Riemersma RA, Macintyre CC, Cawood EH, Prescott RJ, Ruckley CV. Smoking, lipids, glucose intolerance, and blood pressure as risk factors for peripheral atherosclerosis compared with ischemic heart disease in the Edinburgh Artery Study. *Am J Epidemiol* 1992; 135:331-340.
5. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes* 1988; 37:1595-1607.

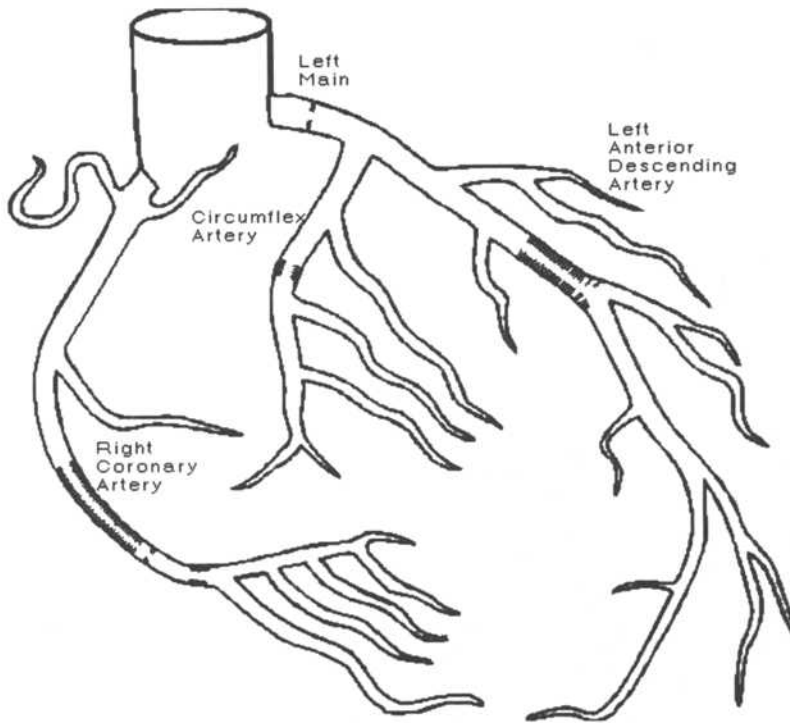


Fig. 3. Electron Beam Computed Tomography (EBCT): coronary diagram of a 68-year-old asymptomatic male with an ABI of 0.8 shows extensive calcium deposits totaling 1000, i.e., coronary calcium score 1000. Coronary angiography (luminography) was recommended.

6. Hoffner SJ, Cassels H. Hyperglycemia as a cardiovascular risk factor. *Am J Med* 2003; 115:6S–11S.
7. Bradby GV, Valente AJ, Walton KW. Serum high-density lipoproteins in peripheral vascular disease. *Lancet* 1978; 2:1271–1274.
8. Gordon D, Probstfield J, Garrison R, et al. High-density lipoprotein cholesterol and cardiovascular risk. *Circulation* 1989; 79:8–15.
9. Caralis DG, Dimitropoulos S. Physical inactivity is a risk factor for LEAD and coronary heart disease. Lower Extremity Arterial Disease (LEAD) Chapter III Epidemiology. Risk Factors. Subchapter 5. Lower Extremity Arterial Disease (LEAD). Caralis DG, Editors, Bakris GL, Co-editor. Humana press:Totowa, NJ 2004.
10. Rubins HB, Robins SJ, Collins D, et al. Diabetes, plasma insulin, and cardiovascular disease. *Arch Intern Med* 2002; 162:2597–2604.
11. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001; 285: 2486–2497.

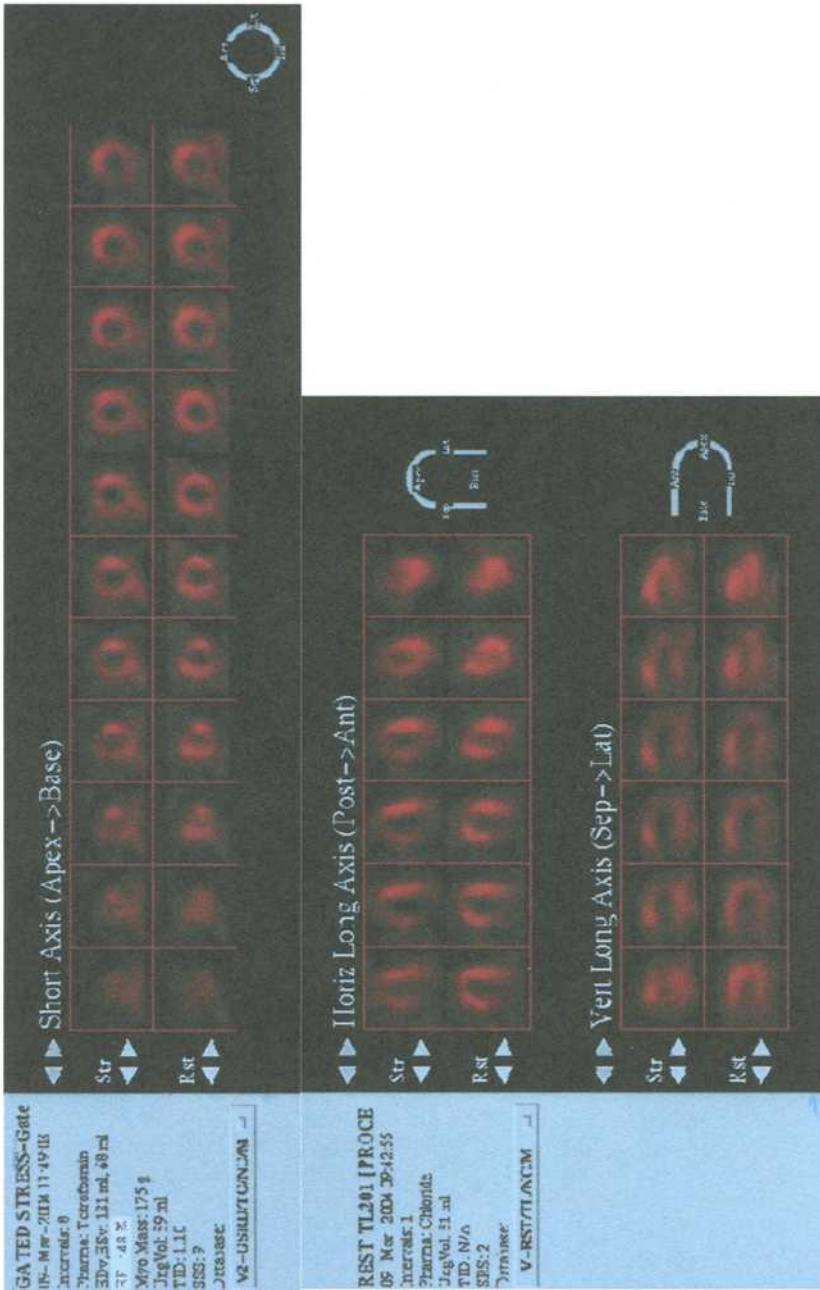


Fig. 4. Abnormal rest/stress myocardial perfusion study of a 69-year-old male with stable infrequent right and left calf claudication. Findings suggest adenosine-induced myocardial ischemia in the distribution of CAD and possibly right coronary artery.

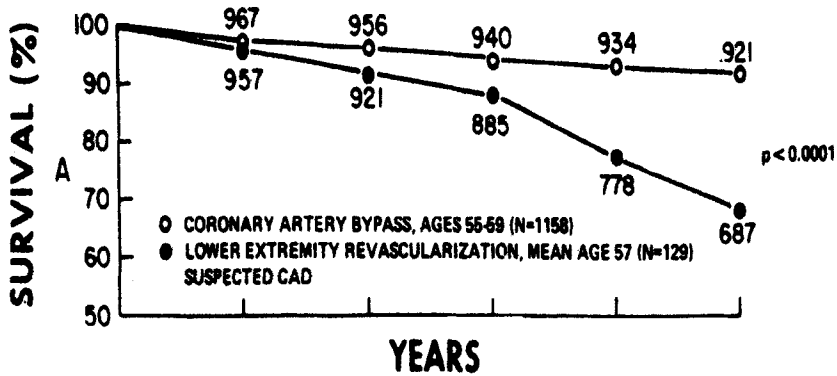


Fig. 5. Survival of patients with LEAD who underwent surgical revascularization procedures compared to patients who had CABG performed. (Adapted from ref. 180.)

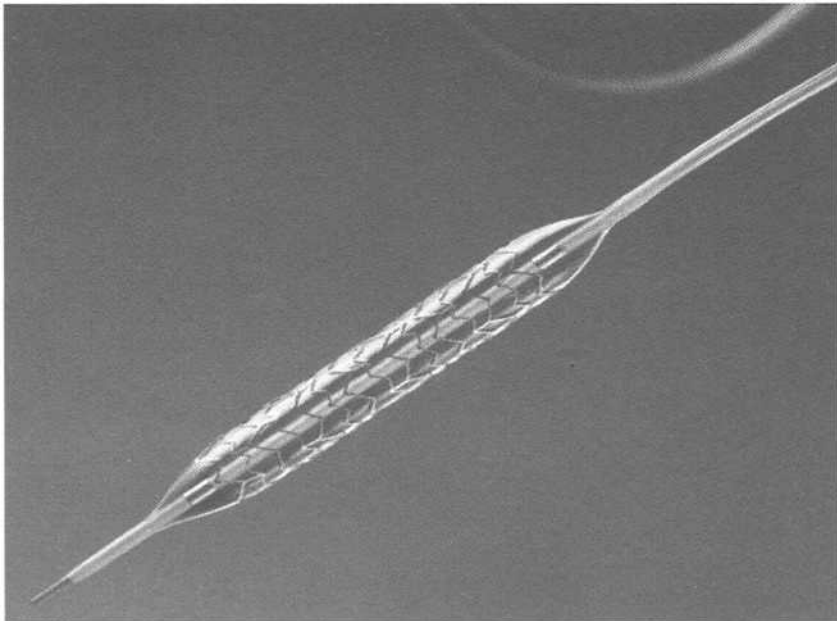


Fig. 6. The majority of percutaneous coronary interventions are performed with drug eluting stents (DES) in order to minimize restenosis, a common phenomenon with balloon angioplasty and even bare metal stents.

12. Fowkes FG, Leng GC, Donnan PT, Deary IJ, Riemersma RA, Housley E. Serum cholesterol, triglycerides and aggression in the general population. *Lancet* 1992; 340:995–998.
13. Riolker PM, Genest J, Libby P. Risk factors for atherogenic disease. In: Braunwald, Zipes, Libby: Heart Disease. 6th ed., vol 1. Philadelphia, London, NY, St. Louis, Sydney, Toronto: W.B. Saunders, 2001; 1016.
14. Hobbs HH, White AL Lipoprotein (a): Intrigues and Insights. *Current Opinion. Lipidology* 1999; 10:225–236.
15. Valentine RJ, Grayburn PA, Vega GL, Grundy SM. Lp(a) lipoprotein is an independent, discriminating risk factor for premature peripheral atherosclerosis among white men. *Arch Intern Med* 1994; 154:801–806.
16. Tyrell J, Cooke T, Reilly M, Colgan M, Moore D, Shanik DG, et al. Lipoprotein [Lp(a)] and peripheral vascular disease. *J Intern Med* 1992; 232:349–352.
17. Ariyo AA, Thach C, Russel T. For the Cardiovascular Health Study Investigators: Lp(a) Lipoprotein, vascular disease, and mortality in the elderly. *New J Med* 2003; 349:2108–2115.
18. Maher VM, Braun BG, Marcovina SM, et al. Effects of lowering LDL cholesterol on the cardiovascular risk of lipoprotein (a). *JAMA* 1995; 274:1771–1774.
19. Kullo IJ, Gau GT, Tajik AJ. Novel risk factor for atherosclerosis. *Mayo Clinic Proceedings* 200; 75:369–380.
20. Brook RD, Weder AB, Grossman PM, Rajagopalan S. Management of Intermittent Claudication. *Cardiology Clinics* 2002; 20:521–534.
21. Kroon AA, van Asten WN, Stalenhoef AF. Effect of apheresis of low-density lipoprotein on peripheral vascular disease in hypercholesterolemic patients with coronary artery disease. *Ann Internal Med* 1996; 125:945–954.
22. Welch GN, Loscalzo J. Homocysteine and atherothrombosis. *N Eng J Med* 1998; 338:1042–1050.
23. Malinow MR, Kang SS, Taylor LM, Wong PW, Couil B, Inahara T, et al. Prevalence of hyperhomocysteinemia in patients with peripheral arterial occlusive disease. *Circulation* 1989; 79:1180–1188.
24. Johnson CL, Rifkind BM, Sempos CT, et al. Declining serum total cholesterol levels among US adults; the National Health and Nutrition Examination Surveys. *JAMA* 1993; 269:3002–3008.
25. Exel E, de Craen AJM, Gussekloo J, et al. Association between high-density lipoprotein and cognitive impairment in the oldest old. *Ann Neurol* 2002; 51:716–721.
26. Welch GN, Loscalzo J. Homocysteine and atherothrombosis. *N Eng J Med* 1998; 338:1042–1050.
27. Rosenson RS, Tangeney CC, Hafner JM. Intraindividual variability of fibrinogen levels and cardiovascular risk profile. *Arteriosclerosis Thrombosis* 1994; 14: 1928–1932.
28. Folsom AR, Wu KK, Rosamond WD et al. Prospective study of hemostatic factors and incidence of coronary heart disease: The Atherosclerosis Risk in Communities (ARIC) study. *Circulation* 1997; 96:1102–1108.
29. Maresca G, Diblasio A, Marchioli R et al. Measuring plasma fibrinogen to predict stroke and myocardial infarction: An update. *Arteriosclerosis Thrombosis and Vascular Biology* 1999; 19:1368–1377.
30. Humphries SE. Genetic regulation of fibrinogen. *Euro Heart J* 1995; 16:19–20.
31. Fowkes FG, Connor JM, Smith FB, Wood J, Donnan PT, Lowe GD, Fibrinogen genotype and risk of peripheral atherosclerosis. *Lancet* 1992; 339:693–696.

32. Koenig W, Sund M, Filipiak B, et al. Plasma viscosity and the risk of coronary heart disease. Results from the MONICA - Augsburg Cohort study, 1984 to 1992. *Arterioscler Thrombosis Vasc Biol* 1998; 18:768–762.
33. Ross R. Atherosclerosis - an inflammatory disease. *N Eng J Med* 1999; 340:115–126.
34. C-reactive protein: a predictor of peripheral artery disease. *Havard Heart Lett* 1998; 8:6–7.
35. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Plasma concentration of C-reactive protein and risk of developing peripheral vascular disease. *Circulation* 1998; 97:425–428.
36. Criqui MN, Fronek A, Barrett-Connor E, et al. The prevalence of peripheral arterial disease in a defined population. *Circulation* 1985; 71:510–515.
37. Criqui MH, Denenberg JO. The generalized nature of atherosclerosis: how peripheral arterial disease may predict adverse events from coronary artery disease. *Vasc Med* 1998; 3:241–245.
38. McKenna M, Wolfson S, Kuller L. The ratio of ankle and arm arterial pressure as an independent predictor of mortality. *Atherosclerosis* 1991; 87:119–128.
39. McKenna M, Wolfson S, Kuller L. The ratio of ankle and arm arterial pressure as an independent predictor of mortality. *Atherosclerosis* 1991; 87:119–128.
40. Vogt MT, McKenna M, Anderson SJ, et al. The relationship between ankle-arm index and mortality in older men and women. *J Am Geriatr Soc* 1993; 41:523–530.
41. Criqui MH, Langer RD, Fronek A, Feigelson HS, Klauber MR, McCann TJ et al. Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med* 1992; 326:381–386.
42. Newman AB, Sutton-Tyrell K, Voget MT, Kuller LH. Morbidity and mortality in hypertensive adults with a Low Ankle/Arm Blood Pressure Index. *JAMA* 1993; 270:487–489.
43. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. *JAMA* 1991; 265:3255–3264.
44. Jernes R, Gaardsting O, Hougard-Jensen K, Backgaard N, Tommesen KH, Schroeder T, Fate AN. Intermittent claudication: outcome and risk factors. *Br Med J* 1986; 293:1137–1140.
45. Violi F, Criqui M, Longoni A, Castiglioni C, A.D.E.P Group. Relation between risk factors and cardiovascular complications in patients with peripheral vascular disease. Results from the A.D.E.P study. *Atherosclerosis* 1996; 120:25–35.
46. Newman AB, Sutton-Tyrell K, Vogt MT, Kuller LH. Morbidity and mortality in hypertensive adults with a low ankle/arm blood pressure index. *JAMA* 1993; 270:487–489.
47. Eagle KA, Rihal CS, Foster ED, et al. Long-term survival in patients with coronary artery disease: Importance of peripheral vascular disease. *J. Am Coll Cardiol* 1994; 23:1091–1095.
48. Criqui MH, Langer RD, Fronek A, Feigelson HS. Coronary disease and stroke in patients with large-vessel peripheral arterial disease. *Drugs* 1991; 42:16–21.
49. Ogren M, Hedblad B, Jungquist G, Isacson SO, Lindell SE, Janzon L. Low ankle-brachial pressure index in 68-year old men: prevalence, risk factors and prognosis. Results from prospective population study “Men born in 1914,” Malmo, Sweden. *Eur J Vasc Surg* 1993; 7:500–506.

50. Dormandy J, Mahir M, Ascady G, Balsano F, De Leeuw P, Blombery P, et al. Fate of the patient with chronic leg ischaemia. A review article. *J Cardiovasc Surg (Torino)* 1989; 30:50–57.
51. Naidu SS, Vlachos HA, Faxon D, et al. Vascular disease independently predicts worse outcome after percutaneous coronary intervention: Results from the NHLBI Dynamic Registry. *J Am Coll Cardiol* 2003; 41:6:3A abstract 1005A–211.
52. Aronow WS, Ahn C. Prevalence of coexistence of coronary artery disease, peripheral arterial disease, and atherothrombotic brain infarction in men and women 62 \geq years of age. *Am J Cardiol* 1994; 74:64–65.
53. Stanford W, Thompson BH, Weiss RM. Coronary artery calcification: clinical significance and current methods of detection. *Am J Roent* 1993; 161:1139–1146.
54. Breen JF, Sheedy PF II, Schwartz RS, et al. Coronary artery calcification detected with ultrafast CT as an indication of coronary artery disease. *Radiology* 1992; 185:435–439.
55. Detrano R, Hsiai T, Wang S, et al. Prognostic value of coronary calcification and angiographic stenosis in patients undergoing coronary angiography. *J Am Col of Cardiol* 1996; 27:285–290.
56. ACC/AHA/SNM Policy Statement: Standardization of cardiac tomographic imaging. The Cardiovascular Imaging Committee, American College of Cardiology; The Committee on Advanced Cardiac Imaging and Technology, Council on Clinical Cardiology, American Heart Association; and Board of Directors, Cardiovascular Council, Society of Nuclear Medicine. *J Nuclear Cardiology* 1994; 1:117.
57. Bunt TJ. The role of a defined protocol for cardiac risk assessment in decreasing perioperative myocardial infarction in vascular surgery. *J Vas Surg* 1992; 15: 626–634.
58. Ellestadt MH. Stress Testing: Principles and Practice. 4th ed., Philadelphia: FA Davis, 1995.
59. Jones NL. Clinical exercise stress testing. 4th ed. Philadelphia: WB Saunders, 1997.
60. Caralis DG, Shaw L, Bilgere B, et al. Application of computerized exercise ECG digitization: Interpretation in large clinical trials. *J Electrocardiol* 1994; 25:101.
61. Von Knorring J, Lepantalo M. Prediction of perioperative cardiac complications by electrocardiographic monitoring during treadmill exercise testing before peripheral vascular surgery. *Surgery* 1986; 99:610–613.
62. Caralis DG, Dotson S, Kern MJ, et al. Intermittent coronary spasm during graded exercise. *Clinical Cardiol* 1992; 15:383–386.
63. Rywik TM, Zink RC, Gittings NS et, al. Independent prognostic significance of ischemic ST Segment response limited to recovery from treadmill exercise in asymptomatic subjects. *Circulation* 1998; 97:2117.
64. Nesto RW, Watson FS, Kowalchuk GJ, et al. Silent myocardial ischemia with peripheral vascular disease: assessment by dipridamole thallium-201 scintigraphy. *Am Heart J* 1990; 120:1073–1077.
65. Zaret BL, Strauss HW, Martin NE, et al. Noninvasive regional myocardial perfusion with radiative potassium. Study of patients at rest, with exercise and during angina pectoris. *N Eng J Med.* 1973; 288:809.
66. Nguyen T, Heo J, Ogilby JD, et al. Single photon emission computed tomography with Thallium-201 during adenosine-induced coronary hyperemia: Correlation with coronary arteriography, exercise thallium imaging and two-dimensional echocardiography. *J Am Col* 1990; 16:1375.
67. Zaret BL, Rigo P, Wackers FJTH, et al. The Tetrofosmin International Trial Study Group: Myocardial perfusion imaging with 99mTc-tetrofosmin. Comparison to

- ²⁰¹Tl imaging and coronary angiography in a phase III multicenter trial. *Circulation* 1995; 91:313.
68. Raby KE, Goldman L, Creager MA, et al. Correlation between preoperative ischemia and major cardiac events after peripheral vascular surgery. *N Eng J Med* 1989; 321:1296–1300.
 69. Sachs RN, Tellier P, Larmignat P, et al. Assessment by dipyridamole-thallium-201 myocardial scintigraphy of coronary risk before peripheral vascular surgery. *Surgery* 1988;103: 584–587.
 70. McPhail NV, Ruddy TD, Calvin JE, et al. A comparison of dipyridamole-thallium imaging and exercise testing in the prediction of postoperative cardiac complications in patients requiring arterial reconstruction. *J Vasc Surg* 1989; 10:51–56.
 71. Lette J, Waters D, Lassonde J, et al. Multivariate clinical models and quantitative dipyridamole-thallium imaging to predict cardiac morbidity and death after vascular reconstruction. *J Vasc Surg* 1991; 14:160–169.
 72. Gould KL. Non invasive assessment of coronary stenoses by myocardial perfusion imaging during pharmacologic coronary vasodilation I. Physiologic basis and experimental validation. *Am J Cardiol* 1978; 41:267.
 73. Hendel RC, Cutler BS, Vilegas BJ, et al. Dipyridamole thallium imaging predicts both perioperative and late cardiac events in vascular patients. *Circulation* 1990; 82:III202.
 74. Levinson JR, Boucher CA, Coley CM, et al. Usefulness of semiquantitative analysis of dipyridamole-thallium-201 redistribution for improving risk stratification before vascular surgery. *Am J Cardiol* 1990; 66:406–410.
 75. McPhail NV, Ruddy TD, Barber GG, et al. Cardiac risk stratification using dipyridamole myocardial perfusion imaging and ambulatory ECG monitoring prior to vascular surgery. *Eur J Vasc Surg* 1993; 7:151–155.
 76. deSilva R, Yamamoto Y, Rhodes CG, et al. Preoperative prediction of the outcome of coronary revascularization using positron emission tomography. *Circulation* 1992; 86:1738.
 77. DiCarli MF, Davidson M, Little R, et al. Value of metabolic imaging with positron emission tomography for evaluating prognosis in patients with coronary artery disease and left ventricular dysfunction. *Am J Cardiol* 1994; 73:527.
 78. Verani MS, Mahmariam J, Hixson JB, et al. Diagnosis of coronary artery disease by controlled coronary vasodilatation with adenosine and Thallium-201 scitigraphy in patients unable to exercise. *Circulation* 1990; 82:80.
 79. Bottcher M, Czernin J, Sun KT, et al. Effect of caffeine on myocardial blood flow at rest and during pharmacologic vasodilatation. *J Nucl Med* 1995; 36:2016.
 80. Cutler BS, Wheeler HB, Paraskos JA, et al. Applicability and interpretation of electrocardiographic stress testing in patients with peripheral vascular disease. *Am J Surg* 1981; 141:501–505.
 81. McCabe CJ, Reidy NC, Abbott WM, et al. The value of electrocardiogram monitoring during treadmill testing for peripheral vascular disease. *Surgery* 1981; 89:183–186.
 82. Gajraj H and Jamieson. Coronary artery disease in patients with peripheral vascular disease. *Br J Surg* 1994; 81:332–342.
 83. Chin JH, Bhatt DL, Moliterno DJ, Ellis SG. Peripheral arterial disease independently predicts higher mortality following percutaneous coronary intervention. *Circulation* 2003; 108:1674.
 84. Chobanian Aram V, Bakris G, Black HR, et al. The seventh report of the Joint National Committee on Prevention, detection, evaluation and treatment of high blood pressure. The JNC 7 Report. *JAMA* 2003; 289:2560–2572.

85. Nissen SE, Tuzcu EM, Schoenhagen P, et al. Effect of intensive compared with moderate lipid lowering therapy on progression of coronary atherosclerosis. A randomized controlled trial. *JAMA* 2004; 291:1071–1080.
86. Cannon CP, Braunwald E, McCabe CH, et al. Comparison of intensive and moderate lipid lowering with statin after acute coronary syndromes. *N Engl J Med* 2004; 350:1495–1504.
87. Malone JM, More WS, Goldstone J. Life expectancy following aortofemoral arterial grafting. *Surgery* 1977; 81:551–555.
88. Cooperman M, Pflug B, Martin EW, Evans WE. Cardiovascular risk factors in patients with peripheral vascular disease. *Surgery* 1978; 84:505–509.
89. Szilagyi ED, Hageman JH, Smith RF, et al. Autogenous vein grafting in femoropopliteal atherosclerosis: the limits of its effectiveness. *Surgery* 1979; 86:836–849.
90. Boden WE. High-density lipoprotein cholesterol as an independent risk factor in cardiovascular disease: assessing the data from Framingham to the Veterans Affairs High-Density Lipoprotein Intervention Trial. *Am J Cardiol* 2000; 86:19L–22L.
91. Inoue T, Saniabadi AR, Matsunaga R, et al. Impaired endothelium-dependent acetylcholine-induced coronary artery relaxation in patients with high serum remnant lipoprotein particles. *Atherosclerosis* 1998; 139: 363–367.
92. Brown WV, Dujovne CA, Farquhar JW, et al. Effects of fenofibrate on plasma lipids. Double-blind, multicenter study in patients with type IIA or IIB hyperlipidemia. *Arteriosclerosis* 1986; 6:670–678.
93. Karpe F, Taskinen MR, Nieminen MS, et al. Remnant-like lipoprotein particle cholesterol concentration and progression of coronary and vein-graft atherosclerosis in response to gemfibrozil treatment. *Atherosclerosis* 2001; 157:181–187.
94. Wang TD, Chen WJ, Lin JW, et al. Efficacy of fenofibrate and simvastatin on endothelial function and inflammatory markers in patients with combined hyperlipidemia: relations with baseline lipid profiles. *Atherosclerosis* 2003; 170:315–323.
95. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin and 20,536 high-risk individuals; a randomized placebo-controlled trial. *Lancet* 2002; 360:7–22.
96. Aronow WS, Ahn C, Gutstein H. Incidence of new atherothrombotic brain infarction to older persons with myocardial infarction and serum low-density lipoprotein cholesterol ≥ 125 mg/dL treated with statin versus no lipid-lowering drug. *J Gerontol A Biol Sci Med Sci* 2002; 57A:M333–M335.
97. Jones PH, Davidson MH, Stein EA, et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR Trial). *Am J Cardiol* 2003; 152–160.
98. Rosenson RS, Tagney CC. Antithrombotic properties of statins: implications for cardiovascular event reduction {Review}. *JAMA* 1998; 279:1643–1650.
99. Spach DH, Dauwens JE, Clark CD, et al. Rhabdomyolysis associated with lovastatin and erythromycin use. *West J Med* 1991; 154:213–215.
100. Oserg K, Bauman JL. QT interval prolongation and torsades des pointes due to erythromycin lactobioante. *Pharmacotherapy* 1995; 15:687–692.
101. Aronow WS, Nayuk D, Woodworth S, et al. Effects of simvastatin versus placebo on treadmill exercise time until the onset of intermittent claudication in older patients with peripheral arterial disease at six months and at one year after treatment. *Am J Cardiol* 2003; 92:711–772.
102. Aronow WS, Nayuk D, Woodworth S, et al. Effects of simvastatin versus placebo on treadmill exercise time until the onset of intermittent claudication. *Circulation* 2003; 108:2557.

103. Burke AP, Farb A, Malcom GT, et al. Plaque rupture and sudden death related to exertion in men with coronary artery disease. *JAMA* 1999; 281:921–926.
104. Koren-Morag N, Tanne D, Graff E, et al. Low-and high-density lipoprotein cholesterol and ischemic cerebrovascular disease. *Arch Intern Med* 2002; 162: 993–999.
105. Weverling-Rijnsburger AW, Jonkers IJ, Exel E, et al. High-density vs low-density lipoprotein cholesterol as the risk factor for coronary artery disease and stroke in old age. *Arch Intern Med* 2003; 163:1549–1554.
106. Mathiesen EB, Bona KH, Joakimsen O. High-density lipoprotein cholesterol are associated with echolucent carotid artery plaques: the Tromo study. *Stroke* 2001; 32:1960–1965.
107. Shah P, Amin J. Low high-density lipoprotein level is associated with increased restenosis rate after coronary angioplasty. *Circulation* 1992; 85:1279–1285.
108. Pearson TA, Bulkley B, Achuff, et al. The association of low levels of HDL cholesterol and arteriographically defined coronary artery disease. *Am J Epidemiol* 1979; 109:285–295.
109. Zuliani G, Romagnoni F, Bollini C, et al. Low levels of high-density lipoprotein cholesterol are a marker of disability in the elderly. *Gerontology* 1999; 45: 317–322.
110. Toth PP. High-density lipoprotein: epidemiology, metabolism, and antiatherogenic effects. *Disease-a-Month* 2001; 47:367–414.
111. Toth PP. Reverse cholesterol transport: high-density lipoprotein's magnificent mile. *Curr Atheroscler Rep* 2003; 5:386–393.
112. Nissen SE, Tsunoda T, Tuzcu EM, et al. Effect of recombinant apoA-1 Milano on coronary atherosclerosis in patients with acute coronary syndromes. A randomized controlled trial. *JAMA* 2003; 290:2292–2300.
113. Aviram M, Hardak E, Vaya J, et al. Human serum paraoxonases (PONI) Q and R selectively decrease lipid peroxides in human coronary and carotid atherosclerotic lesions. *Circulation* 2000; 101:2510–2517.
114. Stremler KE, Stafforini DM, Prescott S, et al. Human platelet-activating factor acetylhydrolase. Oxidatively fragmented phospholipids as substrates. *J Biol Chem* 1991; 266:110,95–11,103.
115. Nofer JR, Levkaus B, Wolinska I, et al. Suppression of endothelial cell apoptosis by high density lipoproteins (HDL) and HDL-associated lysosphingolipids. *J Biol Chem* 2001; 276:4480–4485.
116. Nofer J, Kegrel B, Fobker M, et al. HDL and arteriosclerosis: beyond reverse cholesterol transport. *Atherosclerosis* 2002; 161:1–16.
117. Mineo C, Yuhanna IS, Quon JM, et al. High density lipoprotein-induced endothelial nitric-oxide synthase activation is mediated by Akt and MAP kinases. *J Biol Chem* 2003; 278:9142–9149.
118. Barter P. Inhibition of endothelial cell adhesion molecule expression by high density lipoproteins. *Clin Exp Pharmacol Physiol* 1997; 24:286–287.
119. Lusis AJ. Atherosclerosis. *Nature* 2000; 407:233–241.
120. Aviram M, Brook G. Platelet interaction with high and low density lipoproteins. *Atherosclerosis* 1983; 46:259–268.
121. Fleisher L, Tall A, Witte L, et al. Stimulation of arterial endothelial cell prostacyclin synthesis by high density lipoproteins. *J Biol Chem* 1982; 257:6653–6655.
122. Griffin J, Kojima K, Banka C, et al. High-Density lipoprotein enhancement of anticoagulant activities of plasma protein S and activated protein C. *J Clin Invest* 1999; 3:219–227.
123. Brousseau ME, Schaefer EJ, Wolfe ML, et al. Effects of an inhibitor of cholesteryl-ester transfer protein on HDL cholesterol. *N Eng J Med* 2004; 350:1505–1515.

124. Inazu A, Brown ML, Hesler CB, et al. Increased high-density lipoprotein levels caused by a common cholesteryl-ester transfer protein gene mutation. *N Eng J Med* 1990; 323:1234–1238.
125. Cullen P. Evidence that triglycerides are an independent coronary heart disease risk factor. *Am J Cardiol* 2000; 86:943–949.
126. Assman G, Cullen P, Schutle H. The Munster Heart Study (PROCAM) results of follow-up at 8 years. *European Heart J* 1998; 19:A2–A11.
127. Jeppesen J, Hein HO, Suadicani P, et al. Triglyceride concentration and ischemic heart disease—an eight-year follow-up in the Copenhagen Male study. *Circulation* 1998; 97:1029–1036.
128. Hoakanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. *J Cardiovasc Risk* 1996; 3:213–219.
129. Inoue T, Saniabadi AR, Matsunaga R, et al. Impaired endothelium-dependent acetylcholine-induced coronary artery relaxation in patients with high serum remnant lipoprotein particles. *Atherosclerosis* 1998; 139:363–367.
130. Raven GM. The pathophysiological consequences of adipose tissue insulin resistance. In: *Insulin Resistance: The Metabolic Syndrome X* (Reaven GM and Laws A, eds). Humana Press, Totowa, NJ, 1999; 233–246.
131. Assmann G. Pro and con: High-density lipoprotein, triglycerides, and other lipid subfractions are the future of lipid management. *Am J Cardiol* 2001; 87:2B–7B.
132. Diabetes Association: Management of dyslipidemia in adults with diabetes. *Diabetes Care* 2003; 26:S83–86.
133. Turner RC, Millins H, Neil HA, et al. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom prospective diabetes study (UKPDS:23). *BMJ* 1998; 316:823–828.
134. Stales B, Auwerx J. Regulation of apo-A-I gene expression by fibrates. *Atherosclerosis* 1998; 137:S19–S23.
135. Vu-Dac N, Schoonjans K, Laine B, et al. Fibrates increase human apolipoprotein A-II expression through activation of the peroxisome proliferators-activated receptor. *Clin Invest* 1995; 96:741–750.
136. Bolibar I, von Eckardstein A, Assman G, et al. Short-term prognostic value of lipid measurements for coronary events in patients with angina pectoris. *Thromb Haemost* 2000; 84:955–960.
137. Luc G, Bard JM, Ferrieres J, et al. Value of HDL cholesterol, apolipoprotein A-I, lipoprotein A-I, and lipoprotein A-I/A-II in prediction of coronary heart disease. The PRIME study. *Arterioscler Thromb Vas Biol* 2002; 22:1155–1161.
138. Fruchart JC. Peroxisome proliferators-activated receptor- α activation and high-density lipoprotein metabolism. *Am J Cardiol* 2001; 88:24N–29N.
139. Libby P. Inflammation in atherosclerosis. *Nature* 2002; 420:868–874.
140. Delerive P, De Bosscher K, Bernard S, et al. Peroxisome proliferators-activated receptor α negatively regulates the vascular inflammatory gene response by negative cross-talk with transcription factors. *J Biol Chem* 1999; 274:32,048–32,054.
141. Delerive P, Martin-Nizard F, Chinetti G, et al. PPAR activators inhibit thrombin-induced endothelin-1 production in human vascular endothelial cells by inhibiting the AP-1 signaling pathway. *Circ Res* 1999; 85:394–402.
142. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation* 2002; 22:1135–1143.

143. Ridker PM, Bassuk SS, Toth, PP. C-Reactive protein and risk of cardiovascular disease: evidence and clinical application. *Curr Atheroscler Rep* 2003; 5:341–349.
144. Neve BP, Fruchart JC, Staels B. Roles of the peroxisome proliferators-activated receptors (PPARs) in atherosclerosis. *Biochem Pharmacol* 2000; 60:1245–1250.
145. Robins SJ, Collins D, Wittes JT, et al. VA-HIT Study Group. Veterans Affairs High-Density Lipoprotein Intervention Trial. Relation of gemfibrozil treatment and lipid levels with major coronary events. *JAMA* 2001; 285:1586–1589.
146. Ericsson C-G, Hamsten A, Nilsson J, et al. Angiographic assessment of effects bezafibrate on progression of coronary artery disease in young male postinfarction patients. *Lancet* 1996; 347:849–853.
147. Frick MH, Syvanne M, Nieminen MS, et al. Prevention of the angiographic progression of coronary and vein-graft atherosclerosis by gemfibrozil after coronary bypass surgery in men with low levels of HDL cholesterol. *Circulation* 1997; 96:2137–2143.
148. Rubins HB, Davenport J, Babikian V, et al. Reduction in stroke with gemfibrozil in men with coronary heart and low HDL cholesterol. *Circulation* 2001; 103: 2828–2833.
149. Sudhop T, Lutjohann D, Kodal A, et al. Inhibition of intestinal cholesterol absorption by ezetimibe in humans. *Circulation* 2002; 106:1943–1948.
150. Backman JT, Kyrklund C, Neuvonen M, et al. Gemfibrozil greatly increases plasma concentrations of cerivastatin. *Clin Pharmacol Ther* 2002; 72:685–691.
151. Prueksaritanont T, Zhao JJ, Ma B, et al. Mechanistic studies on metabolic interactions between gemfibrozil and statins. *J Pharmacol Exp Ther* 2002; 301: 1042–1051.
152. Kyrklund C, Backman JT, Kivisto KT, et al. Plasma concentrations of active lovastatin acid are markedly increased by gemfibrozil but not by bezafibrate. *Clin Pharmacol Ther* 2001; 69:340–345.
153. Kyrklund C, Backman JT, Neuvonen M, et al. Gemfibrozil increases plasma pravastatin concentrations and reduces pravastatin renal clearance. *Clin Pharmacol Ther* 2003; 73:538–544.
154. Martin PD, Dane AL, Schneck DW, et al. An open label, randomized, three-way crossover trial of the effects of coadministration of rosuvastatin and fenofibrate on the pharmacokinetic properties of rosuvastatin and fenofibric acid in healthy male volunteers. *Clin Ther* 2003; 25:459–471.
155. Pan WJ, Gustavson LE, Achari R, et al. Lack of a clinically significant pharmacokinetic interaction between fenofibrate and pravastatin in healthy volunteers. *J Clin Pharmacol* 2000; 40:316–323.
156. Crestor product information. AstraZeneca Pharmaceuticals LP, August 2003.
157. Sakai T, Kamana VS, Kashyap V. Niacin, but not gemfibrozil, selectively increases LP-AL, a cardioprotective subfraction of HDL, in patients with low HDL cholesterol. *Arteriosclerosis Thrombosis Vascular Biol* 2002; 22:878.
158. Morgan JM, Capuzzi DM, Baksh RI, et al. Effects of extended-release niacin on lipoprotein subclass distribution. *Am J Cardiol* 2003; 14:298–305.
159. Gray DR, Morgan T, Chretien SD, et al. Efficacy and safety of controlled-release niacin in dyslipoproteinemic veterans. *Ann Intern Med* 1994; 121:252–258.
160. Sakai T, Kamanna VS, Kashyap V. Niacin, but not gemfibrozil, selectively increases LP-AI, a cardioprotective subfraction of HDL, in patients with low HDL cholesterol. *Arterioscler Thromb Vasc Biol* 2001; 21:1783–1789.
161. Ganjji SH, Kamanna VS, Kashyap ML. Niacin and cholesterol: role in cardiovascular disease (review). *J Nutr Biochem* 2003; 14:298–305.

162. McKenney JM, Proctor JD, Harris S, et al. A comparison of the efficacy and toxic effects of sustained vs immediate-release niacin in hypercholesterolemic patients. *JAMA* 1994; 271:672–674.
163. Elan MB, Hunnigake DB, Davis KB, et al. Effect of niacin on lipid and lipoprotein levels and glycemic control in patients with diabetes and peripheral arterial disease. The ADMIT Study: a randomized trial. *JAMA* 2000; 284:1263–1270.
164. Morgan JM, Capuzzi DM, Bakash RI, et al. Effects of extended-release niacin on lipoprotein subclass distribution. *Am J Cardiol* 2003; 91:1432–1436.
165. Grundy SM, Vega GL, McGovern ME, et al. Efficacy, safety and tolerability of once-daily niacin for the treatment of dyslipidemia associated with type 2 diabetes. *Arch Intern Med* 2002; 162:1568–1576.
166. Capuzzi DM, Guyton JR, Morgan JM, et al. Efficacy and safety of an extended-release niacin (Niaspan): a long-term study. *Am J Cardiol* 1998; 82:74U–81U.
167. Schlierf G, Dorow E. Dural patterns of triglycerides, free fatty acids, blood sugar and insulin during carbohydrate-induction in man and their modification by nocturnal suppression of lipolysis. *J Clin Invest* 1973; 52:732–740.
168. Blankenhorn DH, Nessim SA, Johnson RL, et al. Beneficial effects of combined colestipol-niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. *JAMA* 1987; 257:3233–3240.
169. Cashin-Hemphill L, Mack WJ, Pogoda JM, et al. Beneficial effects of colestipol-niacin on coronary atherosclerosis. A 4-year follow-up. *JAMA* 1990; 264:3013–3017.
170. The Coronary Drug Project Research Group. Clofibrate and niacin in coronary heart disease. *JAMA* 1975; 231:360–381.
171. Canner PL, Berge KG, Wenger NK, et al. Fifteen year mortality in coronary drug project patients: long-term benefit with niacin. *J Am Coll of Cardiol* 1986; 8:1245–1255.
172. Graham IM, Daly LE, Refsum HM, et al. Plasma homocystein as a risk factor for vascular disease; the European concerted action project. *JAMA* 1997; 277:1775–1781.
173. Vogel RA, Corretti MC, Plotnick GD. The Postprandial effect of components of the Mediterranean diet on endothelial function. *J Am Coll Cardiol* 2000; 36:1455–1460.
174. Physicians' Desk Reference. Montvale, NJ: Medical Economics Company, Inc., 2000; 1329.
175. Jurgens JL, Barker NW, Hines EA. Arteriosclerosis obliterans: review of 520 cases with special reference to pathogenic and prognostic factors. *Circulation* 1960; 21:188–195.
176. Tomatis LA, Fierens EE, Verbrugge GP. Evaluation of surgical risk in peripheral vascular disease by coronary arteriography: a series of 100 cases. *Surgery* 1972; 71:429–435.
177. Ameli FM, Stein M, Provan JL, et al. Predictors of surgical outcome in patients undergoing aortobifemoral bypass reconstruction. *J Cardiovasc Surg* 1990; 31:333–339.
178. Hertzner NR. Basic data concerning associated coronary disease in peripheral vascular patients. *Ann Vas Surg* 1987; 1:616–620.
179. Hertzner NR, Beven, EG, Young JR, et al. Coronary artery disease in peripheral vascular patients. A classification of 1000 coronary angiograms and results of surgical management. *Ann Surg* 1984; 199:223–233.
180. Crawford ES, Bomberger RA, Glaeser DH, et al. Aortoiliac occlusive disease: factors influencing survival and function following reconstructive operation over a twenty-five year period. *Surgery* 1981; 90:1055–1066.

181. Pasternak RC, Brown LE, Stone PH, et al. Effect of combination therapy with lipid-reducing drugs in patients with coronary heart disease and “normal” cholesterol levels. *Ann Intern Med* 1996; 125:259–540.
182. Jamieson WRE, Janusz MT, Miyagishima RT, et al. Influence of ischemic heart disease on early and late mortality after surgery for peripheral occlusive vascular disease. *Circulation* 1982; 66:192–197.
183. Arous EJ, Baum PL, Cutler BS. The ischemic exercise test in patients with peripheral vascular disease: implications for management. *Arch Surg* 1984; 119:780–783.

10 Medical Therapy of Claudication and Lower Extremity Arterial Disease

*Dennis G. Caralis, MD, PhD, MPH,
FAHA, FACC*

CONTENTS

INTRODUCTION
CILOSTAZOL
AGGRESSIVE RISK FACTOR MODIFICATION
EXTRA-LOW LDL CHOLESTEROL
ANTIPLATELET THERAPY
REFERENCES

INTRODUCTION

The new millennium found lower extremity arterial disease (LEAD) and intermittent claudication in particular, pharmacotherapeutically orphan. Pharmacologically, intermittent claudication has been an orphan since it was first described many decades ago. Intermittent claudication, the cardinal symptom of LEAD occurs in 35 to 50% of patients with known LEAD documented by noninvasive diagnostic methods (1). The development of effective pharmacotherapy for treating claudication has lagged behind that for treating angina pectoris and other manifestations of myocardial ischemia.

The mechanism of the symptoms of claudication has not been well understood and continues to be largely unknown. Claudication may be a manifestation of endothelial dysfunction of segments of the arterial tree of the lower extremities or a manifestation of skeletal muscle

From: *Clinical Hypertension and Vascular Diseases: Lower Extremity Arterial Disease*
Edited by: D. G. Caralis and G. L. Bakris © Humana Press Inc., Totowa, NJ

ischemia or both. In addition to lack of full knowledge of the pathophysiologic mechanisms that precipitate claudication, the methodology used in many clinical trials for the treatment of intermittent claudication was flawed by lack of placebo controls and blinded randomization. Additionally, the series of study patients has been small and the end-points inappropriate (2). The lack of effective pharmacotherapy for decades has allowed LEAD to be considered a surgical disease. The primary care physician after taking a detailed history from the patient and performing a meticulous physical examination, looking for decreased capillary filling time and skin trophic changes, listening for bruits, assessing arterial pulse volumes, and testing for decreased vibratory sensation on the ankles, would then refer the patient for arteriography and subsequently to a vascular surgeon. LEAD is not an isolated, rare disease entity. LEAD affects a large portion of the general population with an age-adjusted prevalence of approximately 12% for men and women older than 40 years of age. The prevalence of intermittent claudication is between 3% and 7% of the general population. In the United States alone the number of patients with LEAD, symptomatic or asymptomatic, is estimated to be between eight and twelve million men and women. Until recently, the clinician would use one venue: history, physical examination → arteriography → vascular surgery. This approach for decades led to the establishment of vascular radiology as a subspecialty and vascular surgery as a major specialty.

For decades LEAD and its cardinal symptom claudication has been pharmacologically in standstill (3,4). The Food and Drug Administration (FDA) has approved only two drugs in the United States, pentoxifylline and cilostazol, to treat claudication in patients with vascular claudication resulting from LEAD. In 1972, a new pharmacologic concept was introduced; a hypothesis really, which stated that if hemorrheology is improved through the stenosed arterial segments by making the erythrocytes more deformable, more pliable and flexible, then claudication should improve. The drug pentoxifylline (Trental) was introduced to treat intermittent claudication based on this hypothesis (5). Much later pentoxifylline was also found to have anti-inflammatory and antiproliferative effects (6,7). In theory, pentoxifylline should improve stable angina pectoris because the same hemorrheologic hypothesis can be applied for the stenosed and diseased coronary arterial segments (5). Pentoxifylline has not been used at any time as an antianginal agent, primarily because of lack of evidence that it is beneficial; the existing series studying pentoxifylline to treat stable angina pectoris are small and inconclusive.

The extensive utilization of pentoxifylline to treat arterial claudication was based on two prospective multicenter, but small clinical trials, which showed that pentoxifylline increases time to absolute claudication (when the patient reports the symptom is so severe, that he/she cannot walk anymore). The walking distance increased after the 24th week of treatment (8–10). Time to absolute claudication is measured in minutes and should be distinguished from time to onset of claudication. Usually, as walking continues claudication gets worse and the patient has to stop to ease off the pressure, the pain, the cramp, the squeezing sensation, the burning, and the other symptoms of claudication. Time to claudication is the time in minutes (or even less) it takes for the onset of claudication. In these two series, time to absolute claudication improved by approximately 20% (8–10) after 24 weeks of treatment. It should be emphasized that pentoxifylline by its mere pharmacologic mode of action on the newly produced red blood cells, takes at least 120 days to manifest its benefits; new erythrocytes produced in the presence of pentoxifylline would be more pliable, flexible, elastic, and deformable. Thus, the hemorrhheologic benefit may manifest itself after the life span of the older erythrocytes ends. The life span of the red blood cells is approximately 120 days. In two meta-analyses of randomized placebo-control trials, pentoxifylline was found to increase walking distance to onset of claudication by approximately 20 to 30 m and distance to absolute claudication by approximately 40 to 50 m (11,13). A more recent meta-analysis showed that the quality of the reported data of all existing trials do not allow any reliable conclusion on the efficacy of pentoxifylline (12) in LEAD. Nonetheless, many patients with LEAD who have been treated with pentoxifylline 400 mg po tid are reluctant to discontinue taking it; some patients attribute the symptomatic improvement of their claudication to pentoxifylline, although detailed interviews by many cardiovascular physicians, including the author, show that in parallel with the initiation of pentoxifylline therapy many, patients with LEAD started engaging in a progressive community based exercise program for at least 30 minutes or more of walking every day, excluding the necessary for symptomatic relief pauses. Today, pentoxifylline is prescribed for certain oncology patients who may benefit from its anti-inflammatory and antimetabolic effect (6,7).

There is skepticism about the efficacy of pentoxifylline (13–15). A meta-analysis concluded that a benefit for pentoxifylline was suggested, but that properly conducted large multicenter trials (would be) required to provide estimate of benefit (11). This meta-analysis (11) estimated a mean improvement in maximal walking distance with pentoxifylline of

48 m (95% confidence interval 18–79 m), similar to the 64 m change with pentoxifylline in the study by Strandness and co-workers (17). In the same study, pentoxifylline was no more effective than placebo.

CILOSTAZOL

In 1999, cilostazol was approved by the FDA specifically for the treatment of intermittent claudication. Cilostazol is a quinolinone derivative that inhibits phosphodiesterase III. The mechanism of action of cilostazol on the symptoms of claudication is not fully understood. Cilostazol and several of its metabolites decrease cyclic adenosine monophosphate (AMP) degradation by inhibiting the enzyme phosphodiesterase III; as a result cyclic AMP concentration increases in both platelets and the vascular wall, leading to decreased platelet aggregation and vascular dilatation (18). Cilostazol can inhibit platelet aggregation introduced by a variety of stimuli including thrombin, ADP, collagen arachidonic acid, epinephrine, and shear stress (19). The effect of cilostazol on circulating plasma lipids has been examined in human volunteers. After 12 weeks as compared to placebo, cilostazol at the dose of 100 mg po bid was associated with a reduction in the serum triglyceride level by about 15% and an increase in HDL-cholesterol by about 10% (19). Cilostazol produces a nonhomogeneous dilatation of vascular beds, with greater dilatation in the femoral arterial beds; it has minimal effect on the vertebral beds, the carotids or superior mesenteric arteries. The renal arterial tree is not responsive to the effects of cilostazol. Cilostazol is not known to have any direct effect on the skeletal myocyte metabolism.

Several prospective randomized trials have reported that cilostazol improves walking distance in patients with intermittent claudication by 40 to 50%, compared to placebo after 12 to 24 weeks of treatment (20,21). One of these placebo-controlled trials evaluated both pentoxifylline and cilostazol (17). Pentoxifylline demonstrated no benefit in either onset of claudication or absolute claudication distance as compared to placebo. Cilostazol, however, significantly improved both distances compared to placebo (17). A prevalent side effect of cilostazol is headache. Transient diarrhea, palpitations, and dizziness have also been reported. The FDA has issued a warning regarding the use of cilostazol in patients with congestive heart failure, because of the increased possibility of sudden cardiac death observed with other forms of diesterase type III inhibitors. Thus, it has become routine practice to assess cardiac function clinically and echocardiographically prior to initiating therapy with cilostazol for claudication, and periodically thereafter. As a result of the modest vasodilatation, heart rate may increase by a mean of 5.1 and 7.4 beats per

minute in patients treated with cilostazol 50 and 100 mg po bid, respectively. In 264 patients evaluated with ambulatory electrocardiogram (ECG) recordings, more cilostazol-treated patients demonstrated an increase in ventricular ectopic activity and nonsustained ventricular tachycardia events (runs of six or less consecutive ventricular ectopic beats), than did placebo-treated patients; these increases of ventricular ectopy were not dose related (23).

A comparison of cilostazol with pentoxifylline for the treatment of intermittent claudication demonstrated a great improvement in walking distance with cilostazol (17). After 24 weeks of treatment, the increase in the absolute claudication distance was 107 m (54%) with cilostazol compared to 64 m (30% increase) seen with pentoxifylline or the placebo effect of 65 m (30%). The beneficial effect of cilostazol on walking distance in claudication patients rapidly dissipates when the drug is withdrawn (24). There was a decline in walking distance with crossover to placebo within 6 weeks; this observation provides support that the initial improvement with cilostazol was caused by the medication's action. Further evidence of clinical benefit with cilostazol is the subjective improvement in walking performance. There was a significant improvement in the physical component scale score of the Medical Outcome Scale Health Survey (SF-36) with cilostazol relative to placebo (18,19). Using the Walking Impairment questionnaire, the cardiovascular physician can see an improvement in the walking speed, walking distance, and in specific measurements of walking difficulties with cilostazol therapy (20,21). Patients with LEAD describe claudication symptoms to have improved at the end of treatment with cilostazol as compared to placebo. A global therapeutic assessment found that significantly more patients rated their outcome as *better* or *much better* with cilostazol compared to placebo (21,25).

Two trials demonstrated an approximate 9% increase in the ankle-brachial index (ABI) with cilostazol (20,26). Although the overall significance of this finding is uncertain, some have suggested that this provides evidence of its vasodilating properties (20,26). A trial involving 516 patients with moderately severe intermittent claudication found that 50 mg of cilostazol given twice daily also improved walking distance with a possible dose response (21). The standard dose for cilostazol is 100 mg po bid. Important pharmacokinetic issues of cilostazol include rapid oral absorption, extensive binding to plasma proteins, 95% hepatic metabolism by cytochrome P450 isoenzymes (especially CYP3A4 or CYP2C19) with formation of active metabolites, and elimination primarily by the renal route (74%) (28). Pharmacokinetic studies have suggested that dose adjustment is not required in renal insufficiency or mild

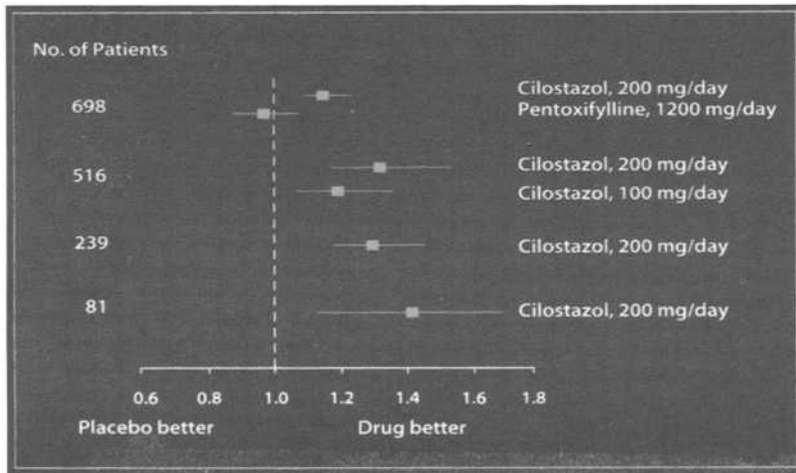


Fig. 1. Geometric mean ratios of the maximal treadmill walking distance (on the horizontal axes) and 95% confidence intervals for cilostazol as compared with placebo. Results of four randomized trials. From ref. 22, with permission.

hepatic impairment, but caution should be exercised in patients with moderate or severe hepatic impairment. Dose adjustments are necessary during co-administration of inhibitors of CYP3A4 or CYP2C19 such as ketoconazole, erythromycin, diltiazem, and omeprazole (28,30).

Side effects of cilostazol have been reported in about 25 to 30% of patients including gastrointestinal cramping, loose bowel movements or diarrhea, headache, dizziness, and palpitations (22). The side effects reported are transient and some appeared to be dose dependent (21). The most common side effect is headache, which is mild and responds well to over-the-counter analgesics. The rate of withdrawal among patients who use cilostazol was similar to those receiving placebo or pentoxifylline (24) (Fig. 1).

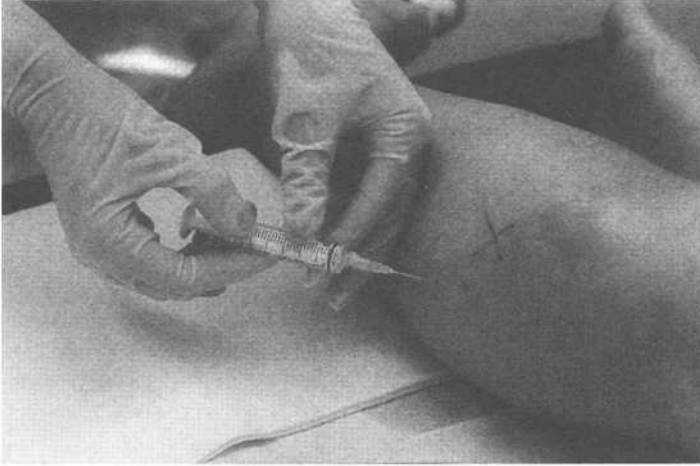
The insert of cilostazol and the *Physicians Desk Reference* contain a *black box* warning that it is contraindicated in patients with congestive heart failure of any severity. As mentioned earlier, this is a caution resulting from the findings with other phosphodiesterase III inhibitors in a subpopulation of patients with congestive heart failure. Oral milrinone that has a significant positive inotropic action, had a detrimental effect on mortality in patients with New York Heart Association class III-IV heart failure (29). Cilostazol has not been adequately studied in patients with congestive heart failure. The long-term effects of phosphodiesterase III inhibitors are not known. It is prudent to evaluate every patient prior to initiating cilostazol therapy both clinically and with echocardiography

looking for congestive heart failure. During therapy with cilostazol periodic evaluations of the heart rhythm and of the cardiac function should be performed, and also an assessment of possible myocardial ischemia silent or symptomatic in view of the fact that on cilostazol the patient with LEAD may be able to walk for a longer distance and become potentially tachycardic. In the United States, clinical trials conducted with more than 2000 patients found no serious adverse effects like myocardial infarction (MI) or mortality attributed to cilostazol for up to 6 months of therapy with it (22). Other phosphodiesterase inhibitors, like NM-702, have shown benefit in increasing walking distance in patients with claudication as a result of LEAD (31).

The effects of propionyl-L-carnitine and L-arginine in claudication owing to LEAD have been tried in small series, but no conclusions have been reported as yet.

Angiogenic growth factors in the treatment of LEAD and intermittent claudication are very promising (32–42). There is ongoing clinical research with angiogenic growth factors, specifically with basic fibroblast growth factor (bFGF) (43) and vascular endothelial growth factor (VEGF) (44). Angiogenesis is the formation of new blood vessels by sprouting from pre-existing vessels. Arteriogenesis is the process of progressive enlargement and remodeling of existing collateral vessels (42). The cellular and molecular mechanisms in angiogenesis are complex and involve a series of steps including cell proliferation, migration, cell–cell and cell–matrix interactions, extracellular matrix turnover, and eventual formation of a primitive capillary tube that then evolves through a process of myocyte and pericyte recruitment into a blood vessel (42).

Angiogenesis is promoted by intramuscular (IM) injections (Fig. 2) in the ipsilateral gluteal, femoral, tibial areas; there appears to be chemotactic affinity between regional ischemia of the limb or limbs and growth factors, which promote angiogenesis. One study (44) suggests that intramuscular gene transfer therapy with phVEGF 165 promotes healing of ischemic ulcers in patients with critical lower extremity limb ischemia. In a more recent study (45), intrafemoral arterial administration of recombinant fibroblast growth factor increased treadmill exercise time significantly compared to placebo. The TRAFFIC study, a randomized trial, is the prototype for other trials of therapeutic angiogenesis (43). Probably the most promising therapeutic angiogenesis is the IM injection of commercially available human, HLA compatible, platelet concentrate into the ischemic limb. Platelets induce collateral vessel formation by supplying VEGF (45). The patient's own platelet concentrate can be injected into the ischemic muscle in order to promote angiogenesis. The IM injection of the patient's own thrombocytes into his or



Intramuscular gene therapy in chronic critical limb ischemia.

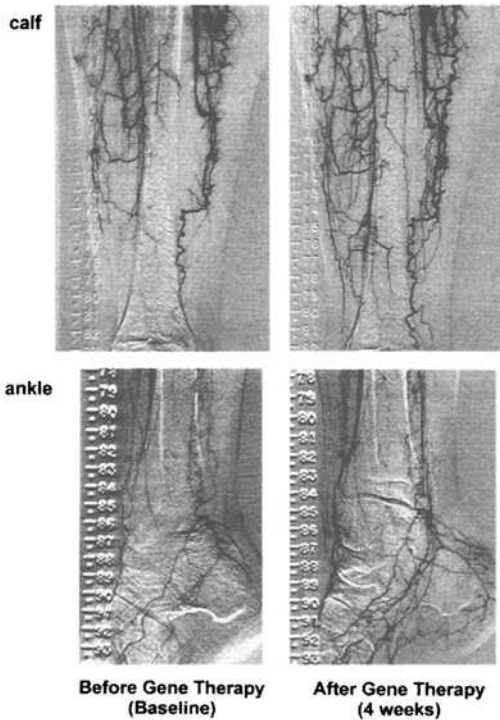


Fig. 2. Serial angiographies after intramuscular gene therapy using phVEGF₁₆₅ showing small-sized newly visible collateral networks at the ankle level. (Coffman JD, Eberhardt RT. Contemporary cardiology. In: Peripheral Arterial Disease. Humana Totowa, NJ, 2003; p. 197.)

her ischemic muscles is becoming a very exciting experience in therapeutic angiogenesis.

AGGRESSIVE RISK FACTOR MODIFICATION

The risk factors associated with atherosclerosis should be aggressively treated in patients with LEAD. *First and foremost is tobacco smoke cessation.* Tobacco use is known to damage vascular endothelial function; it promotes intravascular coagulation and enhances the rate of atherosclerosis progression (46–50,53,54). Cigaret smoking is associated with increased failure rate for percutaneous and surgical revascularization procedures in patients with LEAD. Cigaret smoking in patients with LEAD carries an increased rate of amputations (47–49). Smoking cessation can slow disease progression, reduce the risk of MI and of cardiovascular death (46,49,50). Smoking cessation strategy should include smoking cessation programs and ongoing education from the patient's physician, physician's assistant, family, and friends.

It has been a useful strategy to invite the smoker on a significant date, like his or her birthday, wedding anniversary, or other professional or social event, to announce in front of his family, friends, and business associates, "I am stopping all forms of smoking now. I am quitting *now!*" In preparation for that important date, the smoker's health date, the smoker and their significant other should eliminate all cigaret lighters and other smoking paraphernalia from the home, workplace, and car. The smoker should avoid visiting bars, restaurants, and other areas where smoking is even partially allowed. The spouse of the smoker should suppress smoke odor at home by spraying curtains, furniture, etc. with a pleasant natural aroma .

Nicotine replacement therapy in the form of transdermal nicotine preparations combined with sustained-release bupropion (51) has been successfully tried in some hard core nicotine addicts, after the above social and practical measurements have been taken. The combined therapy of transdermal nicotine and bupropion should last for at least 6 months, and in many cases much longer if the crave to smoke still exists. Sustained-release bupropion therapy alone resulted in a 23.1% tobacco use cessation at one year in a placebo-controlled trial (51). Combination therapy of bupropion and high dose transdermal nicotine has been successful for smoking cessation, but the physician should be certain that his or her patient is not prone to coronary spasm. In premenopausal women, nicotine has been identified as the most important risk factor for coronary spasm (52).

Patients with *diabetes mellitus* have a high relative risk for LEAD, three- to fourfold actually (53,54). Co-existing diabetic neuropathy

increases the risk for dermal ulceration; the symptoms may mimic ischemic rest pain. *Euglycemic control of blood glucose* utilizing both fasting blood sugar samples and hemoglobin A1C assessment should be a key target for every diabetic patient with LEAD. Tight control of blood sugar level prevents small vessel complications of diabetes, but similar benefits on the microcirculation have not been proven at least with today's clinical diagnostic methodologies (56). Large trials of intensive glucose control have shown a reduction in cardiovascular events, including MI, but have not demonstrated a significant reduction in the prevalence of LEAD or amputation. The Diabetes Control and Complication trials compared intensive and conventional insulin therapy in 1441 type 1 diabetics (56). Intensive therapy caused a trend toward reduction in cardiovascular events ($p = 0.08$), but had no effect on the risk for the development of LEAD (56,57). The United Kingdom Prospective Diabetes study (58) evaluated 3867 patients with type 2 diabetes comparing intensive therapy with insulin or sulfonylureas to dietary therapy. Intensive therapy was associated with a trend toward reduction in MI ($p = 0.05$), but had no impact on the risk of death or amputation caused by critical lower limb ischemia (58). Nevertheless, the established benefits of intensive therapy on macrocirculatory diabetic complications include retinopathy, nephropathy, and neuropathy with a trend for reduction in cardiovascular events. Clearly, optimization of serum glucose in patients with LEAD is warranted (59). The goal should be to keep all patients with LEAD euglycemic.

Systemic hypertension, is strongly associated with LEAD (60). The risk of MI and cardiovascular death is increased significantly in patients with LEAD and hypertension (60). Untreated or undertreated hypertension can lead to serious cardiovascular complications. In addition to the strong statistical association between systemic hypertension and cardiovascular events there is pathophysiological evidence as well, i.e., an association between the activation of the renin-aldosterone-angiotensin system and increased risk of adverse cardiovascular events in patients with hypertension (61). The Heart Outcomes Prevention Evaluation (HOPE) trial (62) evaluated the effect of an angiotensin-converting enzyme inhibitor (ACEI), ramipril, on the reduction of adverse cardiovascular events in patients with arteriosclerosis (62). In this study (62), more than 4000 (44%) patients had LEAD, defined as symptoms of intermittent claudication, history of peripheral revascularization procedure or an ABI below 0.9. In the same study (62), 17.7% of individuals in the placebo group died or suffered nonfatal MI or stroke compared to 14.1% of the ramipril treated group; this difference accounts for a 22% reduction of the composite (MI–stroke–death) event risk. There was no

significant difference in the protective effect of ramipril between subjects with LEAD and those without it. The HOPE study (62) emphasizes the importance of including patients with LEAD in studies of secondary prevention of adverse cardiovascular events. Angiotensin-converting enzyme (ACE) inhibition can reduce risk of ischemic events in the LEAD patient population. In diabetic patients with hypertension and LEAD, ACE inhibitors may be beneficial in decreasing the rate of progression of renal dysfunction and overall nephropathy. In patients who cannot tolerate ACE inhibitors well, either as a result of cough mitigated by the bradykinin effect or other side effects, angiotensin receptor blockers (ARBs) have been increasingly utilized: valsartan, losartan, etc., either alone or more preferably combined with a low-dose hydrochlorothiazide or chlorthalidone. Traditionally, the goal and target for blood pressure (BP) control have been set by the Joint National Committee (JNC) on Hypertension. This committee consists of experts on hypertension invited by the National Heart Blood and Lung Institute to confer and come up with recommendations in a consensus forming paper based on existing data. The latest (55) JNC 7 provides a new guideline for hypertension prevention and therapy. The JNC 7 Committee gives us conclusions and important guidelines: (1) in persons older than 50 years, systolic BP of more than 140 mmHg is a much more important cardiovascular disease (CVD) risk factor than diastolic BP; (2) The risk of CVD, beginning at 115/75 mmHg, doubles with each increment of 20/10 mmHg. Individuals who are normotensive at 55 years of age have a 90% lifetime risk for developing hypertension; (3) Individuals with a systolic BP of 120 to 139 mmHg or a diastolic BP of 80 to 89 mmHg should be considered as prehypertensive and require health-promoting lifestyle modifications to prevent CVD; (4) Thiazide-type diuretics should be used in drug treatment for most patients with uncomplicated hypertension, either alone or combined with drugs from other classes. Certain high-risk conditions are compelling indications for the initial use of other antihypertensive drug classes (ACE inhibitors, ARBs, β -blockers, calcium channel blockers); (5) Most patients with hypertension will require two or more antihypertensive medications to achieve goal BP (<140/90 mmHg, or <130/80 mmHg for patients with diabetes or chronic kidney disease); (6) If BP is more than 20/10 mmHg above goal BP, consideration should be given to initiate therapy with two agents, one of which usually should be a thiazide-type diuretic; and (7) The most effective therapy prescribed by the most careful clinician will control hypertension only if patients are motivated. Motivation improves when patients have positive experiences with, and trust in their clinician (55).

EXTRA-LOW LDL CHOLESTEROL

Improvement of the lipid profile is beneficial to all vascular patients with or without demonstrable coronary disease. The goal for the LDL-cholesterol (LDL-C) is to be well below 90 mg/dL or as low as possible, a natural occurrence in parts of China and Japan. The recommendation for an LDL well below 90 mg/dL is based on many large clinical trials utilizing statins. The prevailing trend today based on recently completed large clinical trials is extra-low LDL cholesterol; a median level of 78.9 mg/dL (71) and 62 mg/dL (72). Patients with extra-low cholesterol levels had prospectively fewer cardiac deaths and overall cardiovascular events. The optimal low level of LDL-C is unknown. Analysis of the ARBITER study (73) shows a greater likelihood of regression of atherosclerosis across a broad range of LDL cholesterol values with the greatest likelihood of regression at a LDL-C below 70 mg/dL. Regression of atherosclerosis demonstrated by intravascular ultrasonography (IVUS) imaging in the coronary circulation or in LEAD is an established surrogate for clinical benefit—LDL-C reduction should go well below the current National Cholesterol Education Program (NCEP) (76) value of 100 mg/dL. Regression of carotid atherosclerosis demonstrated by carotid B-mode ultrasound is directly related to the absolute LDL-C level on statin therapy. The greatest regression was obtained with an LDL-C below 70 mg/dL (74).

The axiom should be for all vasculopathic patients with regards to LDL-C: the lower the better.

The goal for high-density lipoprotein cholesterol HDL should be over 40 mg/dL for men and over 50 mg/dL for women. Hypertriglyceridemia, which has been strongly associated with LEAD, should be aggressively treated with weight reduction, exercise, and a high protein–high fiber diet. High protein, high fiber diets, both short-term and long-term, reduce weight significantly and can improve endothelial function by avoiding sugar and animal fat.

Pharmacotherapeutically, a short-acting statin like simvastatin 20 mg as a starting dose after dinner and fenofibrate 160 mg (77) with breakfast has been proven safe and effective for the reduction of triglyceride blood levels and LDL-C. The two pharmacologic agents should be given about 10–12 hours apart to avoid overlap of their half lives and potential liver toxicity. Fibrates should not be co-administered with long-acting statins; the possibility of hepatotoxicity and rhabdomyolysis is real, particularly after a fall resulting into muscle trauma and/or unexpected renal dysfunction.

Long-acting niacin (78–80) in incremental doses at bedtime is very effective and safe in raising HDL-cholesterol. The starting dose can be 500 mg at bedtime the first week, 750 mg the second week, and 1 g or more thereafter. Long-acting niacin should be given after dinner; improving the lipid profile of vascular patients, can also infer clinical benefits and vascular wall benefit, improvement of endothelial function, long-term and short-term. Long-acting niacin (78–80) is safer than short-acting niacin with regard to liver toxicity and should be given after dinner with 325 mg of enteric-coated aspirin, in order to prevent the facial vasodilatation and flashing caused by niacin; smaller doses of aspirin do not prevent flashing. Patient compliance is very important both short-term and long-term. The most common noncompliance side effect of niacin preparations is facial vasodilatation and flashing. Long-acting niacin 500 mg or more combined with a low-dose statin, i.e., 20 mg lovastatin trade name (Advicor) can increase time to claudication and improve lipid profile (author's observations). Raising HDL can inhibit the progression (75) of atherosclerosis.

In a recent study (63), 40 mg of simvastatin significantly increased treadmill exercise time to onset of claudication from baseline by 54 seconds (a 24% increase, $p < 0.0001$) at 6 months after treatment, and by 95 seconds (a 42% increase, $p < 0.0001$) at 1 year of treatment. At 6 months and 1 year after treatment with placebo, treadmill exercise time until onset of intermittent claudication was not significantly different from baseline exercise time (63,69).

In dislipidemic patients with claudication combination therapy with simvastatin 40 mg and ezetimibe (zetia) (70) 10 mg after dinner combined with fenofibrate (77) (Tricor) 160 mg with breakfast, brings a significant improvement in walking time to onset of claudication and time to absolute claudication measured on the treadmill (not yet published data). There is also a remarkable improvement of the patient's lipid profile with this combination therapy.

A combination therapy of rosuvastatin (81) (Crestor) and fenofibrate (Tricor) (77) has been gaining popularity fast among vascular physicians and cardiologists. Rosuvastatin can keep LDL very low and also increase the plasma levels of HDL. Fenofibrate (77) in the morning can bring a dramatic reduction of the serum triglycerides. Rosuvastatin and fenofibrate is a safe combination therapy with regards to liver toxicity and myositis. Nevertheless, it is prudent to periodically evaluate the patient clinically and with liver enzymes and creatine phosphokinases.

Exercise therapy and a heart healthy diet should be preconditions for any long-term pharmacotherapy. A beneficial diet for every vascular

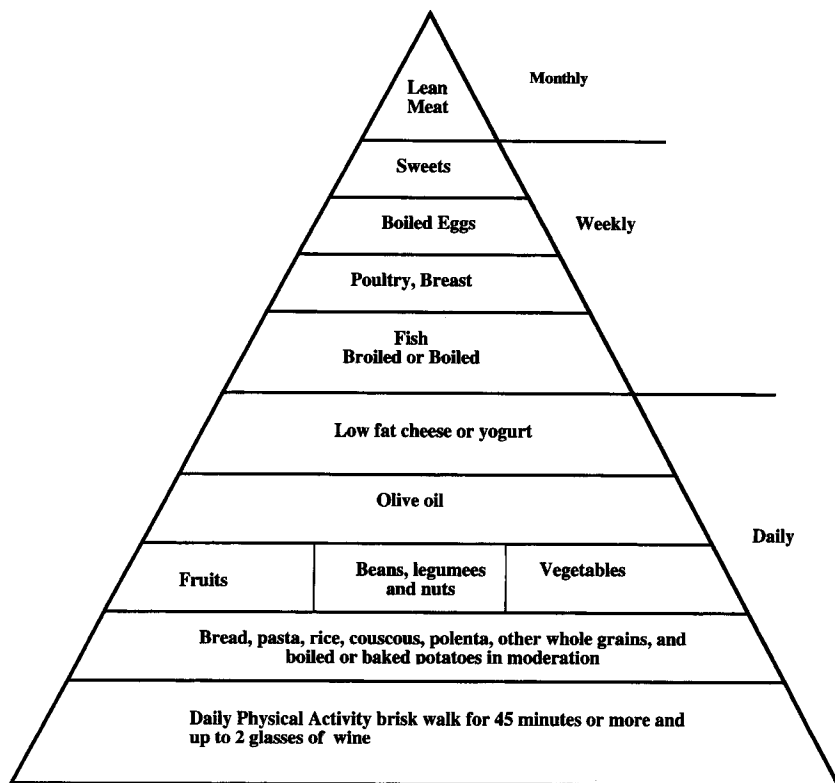


Fig 3. Food Pyramid reflecting the traditional healthy Mediterranean diet. Adapted from Oldways Preservation and Exchange Trust.

patient is the Mediterranean diet, a time honored diet rich in antioxidants (*see* Fig. 3).

ANTIPLATELET THERAPY

Patients with arterial disease caused by atherosclerosis, carotid, coronary, aortic, or LEAD are prone to thrombosis.

In the Peripheral Arterial Disease Detection, Awareness, Risk and Treatment: New Resources for Survival (PARTNERS) study (64), 6979 patients age 70 years or older or age 50–69 years with diabetes mellitus or history of smoking were evaluated by history and ABI. LEAD cases were classified as such, if the ABI was <0.9 or if there was a history of limb revascularization. A main outcome measure evaluated the treatment of LEAD patients compared with other forms of arterial disease.

Although patients with LEAD had similar risk profiles compared to patients with coronary heart disease, antiplatelet medications were recommended less often in patients with newly diagnosed LEAD (35%) and known LEAD (54%) only, compared to 71% of patients with cardiovascular disease only ($p < 0.001$) (64).

Indeed, antiplatelet therapy is underutilized in patients with LEAD. In the Minnesota Regional Peripheral Artery Disease Screening study, 40% of patients with LEAD were receiving no antiplatelet therapy at all (65). A number of landmark studies have concluded that antiplatelet therapy reduces the risk of nonfatal MI, stroke, and cardiovascular death in patients with cardiac and vascular disease. A collaborative meta-analysis of randomized antiplatelet therapy for the prevention of cardiovascular death, MI, and stroke in high-risk patients (66) included more than 135,000 high-risk patients; and the main conclusion was that antiplatelet therapy reduced the risk of adverse cardiovascular events from 13.2% in the control group to 10.7% in the treatment group, a reduction of the odds ratio by 25%. Antiplatelet medications should be recommended for secondary disease prevention in patients with known cardiovascular disease. In a substudy of the same meta-analysis (66), patients with symptomatic LEAD receiving antiplatelet therapy showed a statistically significant reduction (23%) in severe cardiovascular events compared to controls.

The Physicians' Health Study (67) evaluated the effects of aspirin (325 mg/day), compared to placebo in more than 22,000 male physicians over an average treatment period of 5 years. Those in the aspirin group had a 50% reduction of surgical limb revascularization procedures compared to the placebo group; this difference is remarkable. However, the incidence of intermittent claudication was not statistically different in the two groups (aspirin or placebo).

The CAPRIE trial (68) clopidogrel vs aspirin in patients at risk of ischemic events compared the efficacy of clopidogrel (plavix) to aspirin in more than 19,000 patients with atherosclerosis manifested as ischemic stroke, MI, or LEAD defined by an ABI of 0.85 or less, history of revascularization or amputation secondary to ischemia. In the CAPRIE trial, there were more than 6400 patients with LEAD. Clopidogrel was associated with an overall relative risk reduction of 8.7% for adverse cardiovascular events. Patients with LEAD received the greatest benefit, with a relative risk reduction of 23.8% compared to aspirin alone (68).

Patients with LEAD may present with symptoms of intermittent claudication (for a detailed diagnosis and differential diagnosis, *see* Chap-

ter 1). Intermittent claudication can adversely impact the quality of life and impose severe limitations on overall daily activities. Severe arterial stenoses may threaten the viability of the lower extremity, one or both, as a result of critical ischemia necessitating emergent revascularization or even amputation.

Fortunately, the emerging therapeutic angiogenesis and regression therapy of the atherosclerotic plaque burden should turn down the trend for amputation caused by ischemia.

The author's prediction is that in approximately 5 years an amputation will be considered a defeat for the attending physician of the vascular patient.

Medical therapy of claudication and LEAD need a multifaceted approach; aggressive risk factor modification; smoking cessation; body weight reduction; euglycemic control of diabetes optimization of the lipid profile with medications, a heart healthy diet; regression therapy; antiplatelet therapy; angiogenesis; and exercise therapy, community based or supervised at a medical facility. Exercise therapy among its many benefits, reduces high sensitivity C-reactive protein levels as well.

REFERENCES

1. Dormandy JA, Rutherford RB. Management of peripheral arterial disease (PAD). TASC Working Group. *J Vasc Surg* 2000; 31:S1–S296.
2. Cameron HA, Walter PC, Ramsay LE. Drug treatment of intermittent claudication: A critical analysis of the methods and findings of published clinical trials. 1965–1985. *Br J Clin Pharmacol* 1998; 26:569–576.
3. Hirsch AT. Claudication as an “orphan disease” rationale and goals of drug therapy for peripheral arterial disease. *Vasc Med* 1996; 1:37–42.
4. McDermott MM, Mehta S, Liuk, et al. Legs symptoms, the ankle–brachial index, and walking ability in patients with peripheral arterial disease. *J Gen Internal Med* 1999; 14:173–181.
5. Aangelkort B, Spurk P, Habbaba A, et al. Blood flow properties and walking performance in chronic arterial occlusive disease. *Angiology* 1985; 36:285–292.
6. Hansen Pr, Holm AM, Qi JH et al. Pentoxifylline inhibits neointimal formation and stimulates constrictive vascular remodeling after arterial injury. *J Cardiovascular Pharmacology* 199; 34:683–689.
7. Chen YM, Wu KD, Tsai TJ, et al. Pentoxifylline inhibits PDGF-induced proliferation of and TGF-beta-stimulated collagen synthesis by vascular smooth muscle cells. *J Mol Cell Cardiol* 1999; 31:773–783.
8. Peter JM, Cutler BS, Lee BY, et al. Pentoxifylline efficacy in the treatment of intermittent claudication: Multicenter controlled double-blind trial with objective assessment of chronic occlusive arterial disease patients. *Am Heart J* 1982; 104:66–72.
9. Lindgarde F, Labs KH, Rosher M. The pentoxifylline experience: Exercise testing reconsidered. *Vasc Med* 1996; 1:145–154.
10. Linderde F, Jelnesr, Bjorkmen H. et al. Conservative drug treatment in patients with moderatley severe chronic occlusive peripheral arterial disease. Scandinavian Study Group. *Circulation* 1989; 80:1549–1556.

11. Hood SC, Moher D, Barber GG. Management of intermittent claudication with pentoxifylline: meta-analysis of randomized controlled trials. *Can Med Assoc J* 1996; 155:1053–1059.
12. Girolami B, Bernardi E, Prins MH et al. Treatment of intermittent claudication with physical training, smoking cessation, with pentoxifylline or nafronyl: a meta-analysis. *Arch Int Med* 1999; 159:337–345.
13. Radock K, Wyderski RJ. Conservative management of the intermittent claudication. *Ann Int Med* 1990; 113:135–146.
14. Weitz JI, Byrne J, Clagett GP, et al. Diagnosis and treatment of chronic arterial insufficiency of the lower extremities: a critical review. *Circulation* 1996; 94: 3026–3049.
15. Cameron HA, Walker PC, Ramsay LE. Drug treatment of intermittent claudication: a critical analysis of the methods and findings of published clinical trials 1965–1985. *Br J Clin Pharmacol* 1988; 26:569–576.
16. Radack K, Wyderski RJ. Conservative management of intermittent claudication. *Ann Int Med* 1990; 113:135–146.
17. Dawson DL, Cutler BS, Hiatt WR, Hobson RW, Martin JD, Bortey EB, Forbes WP, and Strandness DE. A comparison of cilostazol and pentoxifylline for treating intermittent claudication. *Am J Med* 2000; 109:523–530.
18. Kamiya T, Sakaguchi S. Hemodynamic effects of the antithrombotic drug cilostazol in chronic arterial occlusion in the extremities. *Arzneimitt Eforschung* 1985; 35:1201–1203.
19. Feldman AM, McNamara DM. Reevaluating the role of phosphodiesterase inhibitors in the treatment of cardiovascular disease. *Clin Cardiol* 2002; 25:256–262.
20. Money SR, Herd JA, Isaacsohn JL, et al. Effect of cilostazol on walking distances in patients with intermittent claudication caused by peripheral vascular disease. *J Vasc Surg* 1998; 27:267–274.
21. Beebe HJ, Dawson DL, Cutler BJ. Et al. A new pharmacologic treatment for intermittent claudication; results of a randomized multicenter trial. *Arch Int Med* 1999; 159:2041–2050.
22. Hiatt WR. Medical treatment of peripheral arterial disease and claudication. *N Eng J Med* 2001; 344(21):1608–21.
23. Physicians' Desk Reference. Pletal (cilostazol), 58th ed. 2004; pp. 2500–2503.
24. Dawson DL, DeMaiores CA, Higinio RT, et al. The effect of withdrawal of drugs treating intermittent claudication. *Am J Surg* 1999; 178:141–146.
25. Dawson DL, Cutler BS, Meissner MH, Strandness DE. Cilostazol has beneficial effects in treatment of intermittent claudication: results from a multicenter, randomized, prospective, double blind trial. *Circulation* 1998; 98:678–686.
26. Elam MD, Heckman J, Crouse JR, et al. Effect of the novel antiplatelet agent cilostazol on plasma lipoproteins in patients with intermittent claudication. *Arterioscl Thromb Vasc Biol* 1998; 18:1942–1947.
27. Bramer SL, Forbes WP. Effect of hepatic impairment on the pharmacokinetics of a single dose of cilostazol. *Clin Pharmacokin* 1999; 37:25–32.
28. Mallikaarjun S, Forbes WP, Bramer SL. Effect of renal impairment on the pharmacokinetics of cilostazol and its metabolites. *Clin Pharmacokin* 1999; 37:33–40.
29. Packer M, Carver JR, Rodeneffer RJ, et al. Effect of oral milrinone on mortality in severe congestive heart failure. *N Eng J Med* 1991; 325:1468–1475.
30. Sorkin EM, Markham A. Cilostazol: new drug profile. *Drugs Aging* 1999; 14:63–71.
31. Hiatt WR, Anthony Koda I. Benefit of NM-702, a phosphodiesterase inhibitor in the treatment of claudication presented during the. *Circulation* 2003; abstract 2676.

32. Ferrar N, Houck K, Jakeman L, Louig DW. Molecular and biological properties of the vascular endothelial growth factor family of proteins. *Endocrinol Rev* 1992; 13:18–32.
33. Dvorak HF, Brown LF, Detmar M, Dvorak AM. Vascular permeability factor/vascular endothelial growth factor, microvascular hyperpermeability, and angiogenesis. *Am J Pathol* 1995; 146:1029–1039.
34. Takeshita S, Zheng LP, Ashara T, et al. Therapeutic angiogenesis: a single intra-arterial bolus of vascular endothelial growth factor augments collateral vessel formation in a rabbit ischemic hind limb. *J Clin Invest* 1994; 93:662–670.
35. Thomas KA. Vascular endothelial growth factor, a potent and selective angiogenic agent. *J Biol Chem* 1996; 271:603–606.
36. Pul A, Sniderman AD, Brassard R, Lochapelle KJ, Graham AM, Lisbona R. Enhanced revascularization of the ischemic limb by means of angiogenic therapy. *Circulation* 1993; 88:208–214.
37. Levy PL, Levy NS, Goldberg MA. Post-transcriptional regulation of vascular endothelial growth factor by hypoxia. *J Biol Chem* 1996; 271:2746–2753.
38. Brogi E, Schatteman G, Wu T, et al. Hypoxia-induced paracrine regulation of vascular endothelial growth factor receptor expression. *J Clin Invest* 1996; 97:469–476.
39. Waltenberger J, Mayr V, Pentz S, Hombach V. Functional upregulation of the vascular endothelial growth factor receptor KDR by hypoxia. *Circulation* 1996; 94:1647–1654.
40. Baffour R, Berman J, Garb JL, Rhee SW, Kaufman J, Friedmann P. Enhanced angiogenesis and growth of collaterals by in vivo administration of recombinant basic fibroblast growth factor. *J Vasc Surg* 1992; 16:181–191.
41. Maisonpierre PC, Suric, Jones PF, Bortunkova S. Angioprotein-2, a natural antagonist for Tie2 that disrupts in vivo angiogenesis. *Science* 1997; 277:55–60.
42. Carmeliet P. Mechanisms of angiogenesis and arteriogenesis. *Nat Med* 2000; 6: 389–395.
43. Lederman RJ, Mendel John FO, Anderson RD, et al. Therapeutic angiogenesis with recombinant fibroblast growth factor-2 for intermittent claudication. (the TRAFFIC Study): a randomized trial. *Lancet* 2002; 359:2053–2058.
44. Baumgartner I, Pieczek A, Manor O, et al. Consecutive expression of ph VEGF 165 after intra-muscular gene transfer promotes collateral vessel development in patients with critical limb ischemia. *Circulation* 1998; 97:1114–1123.
45. Iba O, Maturaba H, Takenobu I, Fujiyamas, Masaki H, Okigaki M, I Wasaka T., Implantation of platelets induces collateral vessel formation in a VEGF-dependent manner—new cell source for therapeutic angiogenesis. *Circulation* 2003; Abstract 511.
46. Jonasou T, Bergstrom R. Cessation of smoking in patients with intermittent claudication. Effects on the risk of peripheral vascular complications, myocardial infarction and mortality. *Acta Medical Scandinavica* 1987; 221:253–260.
47. Lassila R, Lepentalo M. Cigarette smoking and the outcome offer lower limb arterial surgery. *Acta Chirurgica Scandinavica* 1998; 154:635–640.
48. Quick CR, Cotton IT. The measured effect of stopping smoking on intermittent claudication. *Br J Surg* 1992; S24–S26.
49. Ingolfsson LO, Sigurdsson G, Sigvaldson H, et al. A marked decline in the prevalence and incidence of intermittent claudication in Icelandic Men. 1968–1986: A strong relationship to smoking and serum cholesterol. The Reykjavik Study. *J Clin Epidemiol* 1994; 47:1237–1243.
50. Faulkner KW, House AK, Casteldan WM. The effect of cessation of smoking on the accumulative survival rates of patients with symptomatic peripheral vascular disease. *Med J Australia* 1983; 1:217–219.

51. Hurt RD, Sacks DP, Glover ED, et al. A comparison of sustained-release bupropion and placebo for smoking cessation. *N Eng J Med* 1997; 337:1195–1202.
52. Caralis DG, Deligonul U, Kern MJ, Cohen JD. Smoking is a Risk Factor for Coronary Spasm in Young Women. *Circulation* 1992; 85:905–909.
53. Foukes FG, Housley E, Riemersma RA, et al. Smoking lipids, glucose intolerance and blood pressure as risk factors for peripheral atherosclerosis compared with ischemic heart disease in the Edinburgh Artery Study. *Am J Epidemiol* 1992; 135:331–341.
54. Murabito JM, D'Agostino RB, Sibley H, et al. Intermittent claudication. A risk profile from the Framingham Heart Study. *Circulation* 1997; 96:44–49.
55. Chobanian AV, Bakris GL, Black HR, Cushman W C, Green LA, Izzo Jr. JL, et al. The seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. The JNC 7 Report. *JAMA* 2003; 289:2560–2572.
56. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Eng J Med* 1993; 329:977–986.
57. Effect of intensive diabetes management of macrovascular events and risk factors in the Diabetes Control and Complications trial. *Am J Cardiol* 1995; 75:894–903.
58. United Kingdom Prospective Diabetes Study Group. Intensive blood-glucose control with sulfonylureas or insulin compared with conventional treatment and risk complications in patients with type 2 diabetes erratum appears in *Lancet*. *Lancet* 1999; 354:602.
59. Orchard TJ, Strandness DE, Jr. Assessment of peripheral vascular disease in diabetes. Report and recommendations of an international workshop sponsored by the American Heart Association and the American Diabetes Association 18–20 September 1992. New Orleans, Louisiana. *Diabetes Care* 1993; 16:1199–1209.
60. Kannel WB, Skinner JJ, Jr., Schwartz MJ, et al. Intermittent claudication. incidence in the Farmingham Study. *Circulation* 1970; 41:875–883.
61. Alderman MH, Madhavan S, Ool WL, et al. Association of the Renin-Sodium profile with the risk of myocardial infarction in patients with hypertension. *N Eng J Med* 1991; 324:1098–104.
62. Yusuf S, Sleight P, Pogue J, et al. Effects of an angiotensin-converting enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Eng J Med* 2000; 342:145–153.
63. Aconow WS, Nayuk D, Woodworth S, and Ahn C. Effects of simvastatin versus placebo on treadmill exercise time until the onset of intermittent claudication in older patients with peripheral arterial disease at six months and at one year after treatment. *Am J Cardiol* 2003; 92:711–772.
64. Hirsch AT, Criqui MN, Treat-Jacobson D, et al. Peripheral arterial disease detection, awareness and treatment in primary care. *JAMA* 2001; 286:1317–1324.
65. Hirsch AT, Halverson SL, Treat-Jacobson D, et al. The Minnesota Regional Peripheral Arterial Disease Screening Program; toward a definition of community standards of care. *Vasc Med* 2001; 6:87–96.
66. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *Br Med J* 2002; 324:71–86.
67. Goldhaber SZ, Manson JE, Stampfer MJ, et al. Low-dose aspirin and subsequent peripheral arterial surgery in the Physicians' Health Study. *Lancet* 1992; 340: 143–145.

68. CAPRIE Steering Committee. A randomized, blinded trial of clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE). *Lancet* 1996; 348: 1329–1339.
69. Aronow WS, Nayak D, Woodworth S, Cahn. Effect of simvastatin versus placebo on exercise time until onset of intermittent claudication. *Circulation* 2003; 108:2557.
70. Harold Bays. Ezetimibe. Expert opinion. *Investigate Drugs* 2002; 11:1587–1601.
71. Nissen SE, Tuzcu EM, Schoenhagen PS, for the REVERSAL Investigators. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis. *JAMA* 2004; 291:107–108.
72. Topol EJ. Intensive statin therapy – A sea change in cardiovascular prevention. *N Eng J Med* 2004; 350:15. www.NEJM.org.
73. Markwood TT, Kent SM, Coyle LC, Flaherty PJ, O'Malley PG, Taylor AJ. Design and rationale of the ARBITER Trial (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol) a randomized trial comparing the effects of atorvastatin on carotid artery intima-medial thickness. *Am Heart J* 2001; 141: 342–347.
74. Kent SM, Coyle LC, Flaherty PJ, Markwood TT, Taylor AJ. Marked low density lipoprotein cholesterol reduction below current national cholesterol education program targets provides the greatest reduction in carotid atherosclerosis. *Clin Cardiol* 2004; 27:17–21.
75. Barter PJ, Brewer HB Jr, Chapman MJ, et al. Cholesteryl ester transfer protein: a novel target for raising HDL and inhibiting atherosclerosis. *Arterioscler Thromb Vasc Biol* 2003; 23:160–167.
76. Expert Panel. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA* 2001; 285(19):2487–2497.
77. Brown WV, Dujovne CA, Farquhar JW, et al. Effects of fenofibrate on plasma lipids. Double-blind, multicenter study in patients with type IIA or IIB hyperlipidemia. *Arteriosclerosis* 1986; 6:670–678.
78. Canner PL, Berge KG, Wenger NK, et al. Fifteen year mortality in coronary drug project patients: long-term benefit with niacin. *J Am Coll of Cardiol* 1986; 8: 1245–1255.
79. Blankenhorn DH, Nessim SA, Johnson RL, et al. Beneficial effects of combined colestipol-niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. *JAMA* 1987; 257:3233–3240.
80. Cashin-Hemphill L, Mack WJ, Pogoda JM, et al. Beneficial effects of colestipol-niacin on coronary atherosclerosis. A 4-year follow-up. *JAMA* 1990; 264: 3013–3017.
81. Jones PH, Davidson MH, Stein EA, et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR Trial). *Am J Cardiol* 2003; 92:152–160.

11

Exercise Therapy for Lower Extremity Arterial Disease

Peter F. Kokkinos, PhD, FACSM, FAHA

CONTENTS

INTRODUCTION
RATIONALE FOR EXERCISE AND THERAPY FOR LOWER EXTREMITY ARTERIAL DISEASE PATIENTS
EXERCISE THERAPY FINDINGS
POTENTIAL MECHANISMS
DESIGNING AN EXERCISE PROGRAM
REFERENCES

INTRODUCTION

Atherosclerosis is a progressive, generalized disease affecting the entire arterial system. The development of atherosclerotic lesions in the large arteries of the lower extremities eventually leads to significant stenosis. Consequently, blood flow distal to the lesions is significantly impaired. The condition is referred to as lower extremity arterial disease (LEAD).

In the early stages of the disease patients are asymptomatic when performing low-intensity daily activities. As the severity of the disease progresses, arterial blood flow distal to the lesions is progressively impaired. Symptoms occur when blood flow requirements to meet the metabolic demand of the lower extremity musculature are not met. The earliest and most frequent presenting symptom is intermittent claudication (aching or cramping) primarily of the calf and thigh muscles during daily activities requiring walking (1,2). The ischemic pain discourages patients from walking or participating in any form of exercise. Conse-

From: *Clinical Hypertension and Vascular Diseases: Lower Extremity Arterial Disease*
Edited by: D. G. Caralis and G. L. Bakris © Humana Press Inc., Totowa, NJ

quently, muscular and cardiovascular capacities deteriorate, fostering an even more sedentary lifestyle, and further deterioration of muscular and cardiorespiratory functions. Limitations in the walking ability of the patients become more evident as the disease progresses and the patient's capacity to perform occupational, leisure, or social activities is severely limited (3,4). It is estimated that the maximal walking distance on a flat surface at 4 km per hour is less than 1000 meters for about 84% of LEAD patients without pain at rest (3). Eventually, patients develop pain at rest.

There is no established pharmacotherapy that is proven efficacious in improving the functional capacity of LEAD patients or resulting in any significant remission in the course of the disease. Only limited pharmacological agents that alter blood rheology (5) and others that improve ischemic skeletal muscle metabolism (6) are available, with limited success in improving physical performance for LEAD patients.

LEAD is classified on the scale of I–IV. The classification is based on symptoms.

- | | |
|-----------|---|
| Class I | Blood flow reduction does not produce visible symptoms and patients are asymptomatic |
| Class II | Intermittent claudication is precipitated by moderate exertion i.e., walking fast, uphill, or distances longer than 200 m |
| Class III | Claudication occur when walking a short distance of approximately 50–100 m |
| Class IV | Ischemic pain occurs at rest |

RATIONALE FOR EXERCISE AND THERAPY FOR LOWER EXTREMITY ARTERIAL DISEASE PATIENTS

Approximately 2500 years ago the ancient Greek physician Hippocrates wrote:

Speaking generally, all parts of the body which have a function if used in moderation and exercised in labors in which they are accustomed, become thereby healthy and well developed and age slowly, but if unused and left idle, they become liable to disease, defective in growth, and age quickly.

These observations were largely forgotten for centuries and the relationship between a physically active lifestyle and health was not recognized until the early 1950s. Since then, a number of large epidemiologic and prospective studies provided consistent and robust evidence that a sedentary lifestyle is deleterious to health. Conversely, physical activity reduces the risk of premature cardiovascular disease and all-cause mortality (7–9) even in patients with established risk factors (10,11). There

is also strong and consistent evidence documenting the protective and therapeutic effects of increased physical activity on the traditional cardiovascular disease risk factors including diabetes, hypertension, and dyslipidemia (12–14). In light of these data, national health organizations including the American Heart Association, American College of Sports Medicine, and the Centers for Disease Control and Prevention strongly recommend that increased physical activity alone or as an adjunct to pharmacologic therapy is implemented for the prevention and management of cardiovascular disease and the aforementioned risk factors (15–17).

LEAD patients often suffer from comorbidities, including hypertension, diabetes mellitus, dyslipidemia, and coronary artery disease. In addition, the sedentary lifestyle fostered by claudication accelerates the deterioration of cardiorespiratory and muscular functions, and leads to a decline in the overall health and quality of life for the LEAD patient (4). Thus, treatment for intermittent claudication should include lifestyle changes for positive modification of the traditional cardiovascular disease risk factors.

Exercise training should be an integral part of such therapeutic approach. An exercise training program of low to moderate intensity can attenuate the deleterious effects of the aforementioned comorbidities associated with LEAD, and provide an attractive and conservative alternative therapy for these patients. For example, walking, the preferred form of exercise for LEAD patients, has a relatively low risk–benefit ratio, it is relevant to daily living, inexpensive, easily implemented to large populations, contributes to the overall health, can be used alone or as an adjunct to pharmacotherapy, and does not interfere with the surgical possibility that may be deemed necessary in the future. In addition, the well-recognized local vasodilatory effects of exercise and the preservation of lean body tissue can only be of benefit to these patients.

EXERCISE THERAPY FINDINGS

The obvious need to improve blood flow to the affected lower extremities in LEAD patients, and the well known local vasodilatory effects of physical work prompted early investigators to assess the possible therapeutic effects of structured exercise programs for these patients. Scientific assessment in patients with mild and moderate claudication began in the 1960s (18–21). In a pioneering study, Hillestad (18) assessed calf muscle blood flow at different workloads. He described the different effects speed and distance had on time to claudication. He also suggested that not only blood flow limitations, but additional fac-

tors are involved in determining the walking performance. Interestingly, the effect of excess weight on walking performance was also assessed, a factor largely ignored by more contemporary investigators. The concepts and findings of this study provided the background and direction for studies that followed.

Exercise rehabilitation is now recommended and implemented as the first line of therapy for LEAD patients in stage I or II alone, in conjunction with medical therapy, and after reconstructive arterial surgery in patients with significant hemodynamic improvements (22). Primarily, two exercise training protocols have been used extensively. One requires the patient to walk to the onset of pain (claudication), rest until the pain subsides, and repeat this intermittent walking several times. The other protocol is similar with the exception that the patients walk until near-maximal or maximal claudication is reached.

Without exception, exercise training studies involving LEAD patients have yielded substantial and clinically significant improvements in walking distance to the onset of pain or maximal pain (18–40). A Meta-analysis of 21 studies revealed that, following exercise rehabilitation, the average walking distance to onset of claudication increased by 179% and the distance to maximal claudication by 122% (23). Significant increases in peak oxygen uptake along with improvements in maximal and pain-free walking time have also been reported (30).

There is also evidence of a synergistic effect when exercise is combined with pharmacologic therapy or reconstructive arterial surgery than either therapy alone. After six months of either antiplatelet therapy, exercise therapy, or a combination of antiplatelet therapy plus exercise, walking distance improved in all groups. However, the greatest improvements were observed in the combined therapy group. Pain-free and maximal walking distances increased by 120% and 105% in the combined therapy group, 90% and 86% in the exercise alone group, and only 35% and 38% in the antiplatelet only group (37).

Exercise training following reconstructive arterial surgery also merits special attention. In one study, patients were randomized to reconstructive surgery, exercise alone, or reconstructive surgery plus exercise. Performance was assessed at baseline and 48 weeks following intervention. The symptom-free and maximal walking distance in the exercise alone group increased by 179% and 151%, respectively. In the surgery only group, the increase was 376% in the symptom-free distance and 173% in the maximal walking distance. In the group that combined surgery with exercise, symptom-free and maximal walking distance increased by 698% and 263%, respectively (35).

The findings of the two studies presented (arterial reconstructive surgery and the antiplatelet therapy) support that a well-implemented exercise program can play an integral role in the therapy of the LEAD patient as an adjunct to either therapy.

Exercise Mode

The mode of exercise for most studies is walking combined with some other forms of leg exercise such as running, cycling, stair climbing, dancing, jumping, and other dynamic and static leg exercises (23). Several studies have also used walking alone and two studies combined and compared walking with resistance (strength) training (31,38). Walking appears to be superior to other forms of exercise training, especially when the exercise protocol requires that patients perform intermittent bouts of walking to near-maximal or maximal pain (24). This is not surprising considering that exercise-induced adaptations are specific to the imposed demand (SAID Principle) and the method of assessing performance (treadmill walking) is similar to the training mode (walking). In other words, in patients whose exercise training consists of walking, performance will be greater and assessments more accurate if they are assessed by a walking test than any other method (i.e., bike test). Greater improvements with walking to near-maximal or maximal pain also suggests that the intensity of the stimulus is directly related to the degree of physiological adaptations.

It is interesting that the efficacy of resistance training as a therapeutic modality for the LEAD patient has been considered in only two studies (31,38). Although both studies reported that resistance training was inferior to walking and no additional benefits to the patient were added when the walking program was supplemented with resistance training, the possible therapeutic effects of resistance exercise for the LEAD patient should not be dismissed.

It is probable that endurance of the leg musculature becomes the limiting factor in LEAD patients after aerobic capacity has improved via a walking program. This is supported by recent findings suggesting that aerobic capacity in the elderly may be compromised by muscle weakness and decline in muscle mass and strength (41–43), characteristics also exhibited by LEAD patients (44).

The failure of the two studies to yield favorable findings may be explained, at least in part, by the resistance training protocol used in these studies. It is important to note that both studies implemented high resistance to reach maximal fatigue of the lower extremity muscles within five to six repetitions. Such training is more conducive to muscular

strength rather than endurance gains. Yet, most daily activities for healthy individuals, and perhaps more so for the LEAD patients, require muscular endurance rather than muscular strength. Therefore, if resistance training is considered as an adjunct to a walking exercise program (aerobic component) for the LEAD patient, it should include resistance training with high repetitions (15–20) and low weight. Such an exercise program is more conducive to muscular endurance rather than strength, and reflects more closely the demands of daily living activities. The findings of a recent study supports that such a program can enhance the ability of LEAD patients to perform daily activities. Healthy adults between the ages of 60 and 83 participated in a 6-month resistance training exercise program consisting of 8 (low) and 13 (high) repetitions. Gains in aerobic capacity and treadmill time to exhaustion were higher in the group that trained with high repetitions (45).

Evidence also supports that in certain conditions glycolytic pathways may play an integral role in the performance of the LEAD patients. Undoubtedly, improved oxidative metabolism will be of benefit for a certain period of exercise duration and intensity. However, at increased workloads (i.e., faster or uphill walk) the demand on the glycolytic pathways also increases. A compromised capacity of type IIa (glycolytic) and the intermediate IIb (oxidative-glycolytic) muscle fibers will lead to greater lactate accumulation at the local level and subsequent claudication pain, forcing the patient to stop (36). The type II fibers respond better to forceful muscle actions that largely depend on anaerobic energy metabolism (46). Therefore, it is likely that challenging the muscle groups of the lower extremities via high-repetition resistance training will improve the glycolytic capacity of the type IIa and IIb fibers, enhance muscular endurance, and ultimately improve the ability of LEAD patients to perform daily tasks.

Intensity

The intensity of the exercise programs is not well described in any of the studies. It is assumed that the exercise intensity depends on the onset of claudication pain (38). It is estimated that only 16% of patients who do not experience pain at rest can walk a distance of 1000 m or more on a flat surface at 4 km/hour or 2.5 miles/hour (3). The average metabolic equivalent (MET) level calculated from the studies included in the meta-analysis was about 3.8 (23). Collectively, this information supports an exercise intensity of approximately 2–4 miles/hour walking speed on a flat surface (47).

Duration and Frequency

In recent studies, the exercise duration was 30 to 60 minutes per session and some reported an exercise duration of 30 minutes or less. Improvements in the onset of claudication pain and maximal claudication pain walking distances are significantly greater in patients exercising 30 or more minutes per session when compared to those exercising less. There is also evidence to support that exercising three or more sessions per week yields greater improvements in claudication distance when compared with fewer than three times per week (23). Thus, it appears that most improvements in physical performance for LEAD patients occur when exercising for at least 90 minutes per week. However, the interaction between duration and frequency cannot be discerned from the existing literature.

Length of the Training Program

Several studies used exercise programs of at least 6 months in duration and approximately as many studies trained the patients for less than 6 months. Improvements in walking distance were noted even after four weeks of training. However, longer training periods are clearly more successful. Greater improvements in walking distances were associated stronger with the length of training lasting 6 months or longer (23).

Limitations in Exercise Studies

The findings of exercise studies make a strong and convincing argument that exercise training is an efficacious therapy for the LEAD patient. Although the consistently favorable findings reported thus far favor an optimistic view, it is necessary to recognize that serious design flaws exist. In several studies, the number of patients studied is relatively small (19,20,25,27,32,37) and, therefore, the statistical power of the studies is compromised. In addition, a control group has not been used in a number of studies (3,20,21,24,40). There is also considerable variability in the distance walked among the exercise studies. For example, the increase in distance to onset of pain ranged from 72 to 746% and to maximal pain 61 to 739% (23). Part of the wide variation may be explained by differences in criteria used to terminate the test (18), and the use of handrails for support during the test, with greater variability when the patients use handrails to support their walking (20,48). In addition, differences in the components of exercise programs used (22) and graded vs constant-load protocols with the former yielding less variability for both initial and maximal claudication distance (18,49,50).

Finally, despite the aforementioned limitations of previous studies, the overwhelming improvements in performance following exercise training strongly suggest that exercise training is an attractive, efficacious therapy for LEAD patients. Previous study limitations do no more than underscore the need for more well-controlled exercise studies in this area.

POTENTIAL MECHANISMS

Various mechanisms have been proposed to explain the improvement in walking distance following exercise training. The compromised blood flow to the lower extremities in LEAD patients and the well-known vasodilatory effects of exercise deserve attention.

Peak arterial blood flow to the symptomatic limb during exercise is 25 to 40% of that observed in the asymptomatic limb (18). This suggests that reduction in exercise performance and peak oxygen uptake in LEAD patients may be explained by the decrease in arterial blood flow (51). The significant increase in maximal arterial blood flow to the calf muscle following reconstructive arterial surgery and its association to improvements in walking distance lends further support to the blood flow theory (35). However, findings on leg blood flow changes following exercise training are inconsistent. Some investigators reported a significant relationship between blood flow changes and walking performance (20,21). The average maximal blood flow increase to the calf following exercise training is 19% and the ankle-brachial index or the ratio of systolic blood pressure measured in the ankle and arm increase is 7% (34–37). Others, however, found either no increase in peak blood flow or no significant relationship between blood flow and improvements in exercise performance (3,25,26,30,36,37).

Despite the inconsistencies in exercise-induced blood flow increases, even small changes in blood flow are likely to play a favorable part in performance. However, it is not likely that the relatively small increase of 19% in blood flow can account entirely for the large increases in walking performance reported, suggesting that improvements in other physiological systems may be involved. This is supported by the significantly greater improvement in performance achieved when physical training was added to patients following reconstructive arterial surgery (35).

In healthy subjects, aerobic exercise training leads to an increase in oxidative enzyme activity and an increase in the capacity of the involved musculature to perform aerobic work (52). In addition, the number and size of mitochondria and capillary density increase resulting in a more

efficient use of oxygen (53,54). Greater utilization of oxygen as a result of higher concentration of oxidative enzymes (25,32,36) and decreased reliance on anaerobic metabolism (40) have also been proposed as adaptations resulting from exercise training in LEAD patients. Mitochondrial and glycolytic enzymes were assessed at baseline and 6 months following therapy in LEAD patients randomized to either exercise training alone, reconstructive arterial surgery, or surgery supplemented with exercise. Relatively high mitochondrial enzyme activity was observed at baseline in all patients suggesting a compensatory response for the compromised blood flow. The enzymatic activity was positively correlated with the maximal walking performance. Following therapy, the metabolic adaptations were reversed in the surgery-only group, but remained high in the surgery plus exercise group. In the exercise only group, however, muscle enzyme activities of cytochrome-c-oxidase, citrate synthase, and 3-OH-acyl-CoA-dehydrogenase were increased beyond baseline. The increased enzymatic activity was correlated with improvements in symptom-free walking performance. Thus, improved local muscle metabolism with increased oxidative capacity may explain why aerobic exercise training improves walking performance in LEAD patients. This suggests a causal relationship (36).

Improved hemorrheological properties (28) and improvement in walking efficiency (55) are consistent with exercise training and have been suggested as possible contributing factors in the improved walking performance of the LEAD patients.

In summary, the mechanisms responsible for the exercise-induced improvements in walking distance remain illusive. The decline in physical performance observed in LEAD patients is likely the collective outcome of deterioration on several physiological systems. Likewise, the exercise-induced improvements in the functional capacity of these patients is the result of favorable changes in several of these systems.

DESIGNING AN EXERCISE PROGRAM

The exercise program for the LEAD patient must be tailored to meet the needs and abilities of the individual patient. Existing comorbidities in certain patients should be considered. Ultimately, the purpose of the exercise program should be to minimize the risk–benefit ratio.

Exercise Mode

The preferred mode of exercise should be walking. However, activities that involve the large muscles of the legs (cycling, stair climbing, tennis, dancing, etc.) can be implemented in the exercise program. Such

approach can improve participation and reduce the attrition rate. In addition, supplementing walking with some resistance training exercises for the lower extremity muscles should be considered. Such a program should emphasize relatively low resistance and high repetitions (15–25 repetitions) performed one to two times per week.

Frequency

The frequency of an exercise program should be at least two times per week for the first two weeks and progressively increase to three to five times per week. Exercise sessions should be performed in nonconsecutive days when possible. It is also essential to recognize that more frequent exercise sessions may increase the incidence of musculoskeletal injuries and reduce compliance.

Duration

The cumulative duration of exercise of 30–60 minutes per session is preferred. Longer exercise durations offer added benefits. However, benefits diminish substantially beyond 60 minutes, while the risk of musculoskeletal injuries increases, compliance decreases.

For those unable to sustain longer exercise periods, intermittent bouts can also be implemented at different times throughout the day. For those with low cardiorespiratory fitness, the duration of exercise can begin at any duration level with rest between bouts. The duration can increase progressively over a period of weeks until the desired goal is achieved. The rate of progression should be specific for each patient.

Intensity

Intensity is difficult to define. Improvements in performance have been noted when patients exercise at intensities that elicit the manifestation of claudication. However, greater improvements have been reported when patients exercise at intensities eliciting maximum or near-maximum pain. However, the interaction between intensity and duration has not been assessed. The average MET level of the studies included in the meta-analysis is 3.8 (23). Although the pain threshold is likely to vary among patients, it is recommended that patients push to the intensity that elicits maximal or near maximum claudication pain.

Rate of Progression

Individual goals and baseline cardiorespiratory fitness and other patient characteristics should be considered when determining the rate of progression. Initial changes in progression should be relatively slow.

Gradual increases should be emphasized in the duration and frequency of exercise rather than intensity. An increase in the weekly duration of no more than 10% is relatively safe for most patients.

Risks Associated With Exercise

The risk of cardiovascular events during physical activity in patients with underlying cardiovascular disease and especially those who are habitually sedentary is significant (56). The risk of a cardiovascular event in LEAD patients has not been assessed. However, it is prudent to assume that these patients are at a relatively high risk. Thus, the initial phase of exercise training should be supervised by trained personnel.

REFERENCES

1. Zatina MA, Berkowitz HD, Gross GM, Maris JM, Chance B. ³¹P nuclear magnetic resonance spectroscopy: Noninvasive biomechanical analysis of the ischemic extremity. *J Vasc Surg* 1986; 3:411–420.
2. Holm S, Bylund-Fellenius AC. Continuous monitoring of oxygen tension in human gastrocnemius muscle during exercise. *Clin Physiol* 1981; 1:541–552.
3. Ekroth R, Dahllof A-G, Gundevall B, Holm J, Schersten T. Physical training of patients with intermittent claudication: Indications, methods, and results. *Surgery* 1978; 84:640–643.
4. Regensteiner JG, Steiner JF, Panzer RJ, Hiatt WR. Evaluation of walking impairment by questionnaire in patients with peripheral arterial disease. *J Vasc Med Biol* 1990; 2:142–152.
5. Porter JM, Cutler BS, Lee BY, Reich T, Reichle FA, Scorgin JT, Strandness DE. Pentoxifylline efficacy in the treatment of intermittent claudication: Multicenter controlled double-blind trial with objective assessment of chronic occlusive arterial disease patients. *Am Heart J* 1982; 104:66–72.
6. Brevetti G, Perna S, Sabba C, Rossini A, Scotto di Uccio V, Berardi E, Godi L. Superiority of L-propionyl carnitine vs L-carnitine in improving walking capacity in patients with peripheral vascular disease: An acute, intravenous, double-blind, cross-over study. *Eur Heart J* 1992; 13:251–255.
7. NIH Consensus Development Panel on Physical Activity and Cardiovascular Health. Physical activity and cardiovascular health. *JAMA* 1996; 276:241–246.
8. Manson JE, Greenland, P, LaCroix AZ, et al. Walking compared with vigorous exercise for the prevention of cardiovascular events in women. *N Engl J Med* 2002; 347(10):716–725.
9. Tuomilehto J, Lindstrom J, Eriksson J, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001; 344:1343–1350.
10. Myers J, Prakash M, Froelicher V, Partington S, Atwood E. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med* 2002; 346:793–801.
11. Tanasescu M, Leitzmann MF, Rimm EB, Hu, FB. Physical activity in relation to cardiovascular disease and total mortality among men with type 2 diabetes. *Circulation* 2003; 107:2435–2439.
12. Diabetes Prevention Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; 346:393–403.

13. Kokkinos P, Narayan P, Papademetriou V. "Exercise as Hypertension Therapy" *Cardiology Clinics* 2001; 19:507–516.
14. Kokkinos P, Fernhall B. Physical activity and high density lipoprotein cholesterol levels: What is the relationship? *Sports Medicine* 1999; 28:307–314.
15. Pate RR, Pratt M, Blair SN. Physical activity and public health: A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. *JAMA* 1995; 273:402–407.
16. American College of Sports Medicine. The recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness in healthy adults. *Med Sci Sports Exerc* 1998; 30:975–991.
17. Fletcher GF, Balady G, Amsterdam EA, et al. Exercise standards for testing and training: A statement for healthcare professionals from the American Heart Association. *Circulation* 2001; 104:1694–1740.
18. Hillestad LK. The peripheral blood flow in intermittent claudication. IV. Significance of the claudication distance. *Acta Med Scand* 1963; 173:467–478.
19. Larsen OA, Lassen NA. Effect of daily muscular exercise in patients with intermittent claudication. *Lancet* 1966; 2:1093–1095.
20. Skinner JS, Strandness, DE. Exercise and intermittent claudication. *Circulation* 1967; 36:23–29.
21. Alpert JS, Larsen A, Lassen NA. Exercise and intermittent claudication: Blood flow in the calf muscle during walking studied by the Xenon-133 method. *Circulation* 1969; 39:353–359.
22. Gardner AW. Exercise training for patients with peripheral arterial disease. In: Thompson PD, eds. *Exercise and Sports Cardiology*. McGraw-Hill Medical Publishing Division, 2001, pp. 371–401.
23. Gardner AW, Poehlman ET. Exercise rehabilitation programs for the treatment of claudication pain: A meta-analysis. *JAMA* 1995; 274:975–980.
24. Carter SA, Hamel ER, Paterson JM, Snow CJ, Mymin D. Walking ability and ankle systolic pressures: observations in patients with intermittent claudication in a short-term walking exercise program. *J Vasc Surg* 1989; 10:642–649.
25. Dahllof A-G, Bjorntorp P, Holm J, Schersten T. Metabolic activity of skeletal muscle in patients with peripheral arterial insufficiency. *Eur J Clin Invest* 1974; 4: 9–15.
26. Dahllof A-G, Holm J, Schersten T, Sivertsson R. Peripheral arterial insufficiency: Effect of physical training on walking tolerance, calf blood flow, and blood flow resistance. *Scand J Rehab Med* 1976; 8:19–26.
27. Ericsson B, Haeger K, Lindell SE. Effect of physical training on intermittent claudication. *Angiology* 1970; 21:188–192.
28. Ernst EE, Matrai A. Intermittent claudication, exercise, and blood rheology. *Circulation* 1987; 76:1110–1114.
29. Feinburg RL, Gregory RT, Wheeler JR, Snyder SO, Gayle RG, Parent FN, Patterson RB. The ischemic window: A method for the objective quantification of the training effect in exercise therapy for intermittent claudication. *J Vasc Surg* 1992; 16:244–250.
30. Hiatt WR, Regensteiner JG, Hargarten ME, Wolfel EE, Brass EP. Benefit of exercise conditioning for patients with peripheral arterial disease. *Circulation* 1990; 81:602–609.
31. Hiatt WR, Wolfel EE, Meier RH, Regensteiner JG. Superiority of treadmill walking exercise vs strength training for patients with peripheral arterial disease. *Circulation* 1994; 90:1866–1874.
32. Holm J, Dahllof A-G, Bjorntorp P, Schersten T. Enzyme studies in muscles of patients with intermittent claudication: Effect of training. *Scand J Clin Lab Invest* 1973; S128:201–205.

33. Jonason T, Ringqvist I. Effect of training on post-exercise ankle blood pressure reaction in patients with intermittent claudication. *Clin Physiol* 1987; 7:63–69.
34. Lepantalo M, Sundberg S, Gordin A. The effects of physical training and flunarizine on walking capacity in intermittent claudication. *Scand J Rehab Med* 1984; 16:159–162.
35. Lundgren F, Dahllof A-G, Lundholm K, Schersten T, Volkmann R. Intermittent claudication- surgical reconstruction or physical training? *Ann Surg* 1989; 209: 346–355.
36. Lundgren F, Dahllof A-G, Schersten T, Bylund-Fellenius AC. Muscle enzyme adaptation in patients with peripheral arterial insufficiency: Spontaneous adaptation, effect of different treatments and consequences on walking performance. *Clin Sci* 1989; 77:485–493.
37. Mannarino E, Pasqualini L, Innoncente S, Scricciolo V, Rignanese A, Ciuffetti G. Physical training and antiplatelet treatment in stage II peripheral arterial occlusive disease: Alone or combined? *Angiology* 1991; 42:513–521.
38. Regensteiner JG, Steiner JF, Hiatt WR. Exercise training improves functional status in patients with peripheral arterial disease. *J Vasc Surg* 1996; 23:104–115.
39. Regensteiner JG, Meyer TJ, Krupski WC, Cranford LS, Hiatt WR. Hospital vs home-based exercise rehabilitation for patients with peripheral arterial occlusive disease. *Angiology* 1997; 48:291–300.
40. Ruell PA, Imperial ES, Bonar FJ, et al. The effect of physical training on walking tolerance and venous lactate concentration. *Eur J Appl Physiol* 1984; 52:420.
41. Frontera WR, Meredith CN, O'Reilly KP, Evans WJ. Strength training and determinants of VO₂max in older men. *J Appl Physiol* 1990; 68:329–333.
42. Braith RW, Vincent KR. Resistance exercise in the elderly person with cardiovascular disease. *Am J Geriatr Cardiol* 1999; 8:63–79.
43. Flegg JL, Lakatta, EG. Role of muscle loss in the age-related associated reduction in VO₂max. *J Appl Physiol* 1988; 65:1147–1151.
44. Regensteiner JG, Wolfel EE, Brass EP, Carry MR, et al. Chronic changes in skeletal muscle histology and function in peripheral arterial disease. *Circulation* 1993; 87:413–421.
45. Vincent KR, Braith RW, Feldman RA, Kallas, HE, Lowenthal DT. Improved cardiorespiratory endurance following 6 months of resistance exercise in elderly men and women. *Arch Intern Med* 2002; 162:673–678.
46. Karlsson JB, Sjodin B, Thorstensson A, Hulten B, Frith K. LDH isozymes in skeletal muscles of endurance and strength trained athletes. *Acta Physiol Scand* 1975; 93:150–156.
47. Ainsworth BE, Haskell, WL, Leon AS, Jacobs, DR, Montoye HJ, Sallis JF, Paffenbarger RS. Compendium of physical activities: Classification of energy costs of human physical activities. *Med Sci Sports Exer* 1993; 25: 71–80.
48. Gardner AW, Skinner JS, Smith LK. Effects of handrail support on claudication and hemodynamic responses to a single-stage and progressive treadmill protocols in peripheral vascular occlusive disease. *Am J Cardiol* 1991; 68:99–105.
49. Gardner AW, Skinner JS, Cantwell BW, Smith LK. Progressive vs single-stage treadmill tests for evaluation of claudication. *Med Sci Sports Exerc* 1991; 23: 402–408.
50. Hiatt WR, Regensteiner JG, Hargarten ME, Hossack KF. The evaluation of exercise performance in patients with peripheral vascular disease. *J Cardiopulmonary Rehab* 1988; 12:525–532.
51. Green S, Mehlsen J. Peripheral Arterial Disease. In Saltin B, Boushel R, Secher N, Mitchell J, eds. *Exercise and Circulation in Health and Disease*. Champaign Il., Human Kinetics, 2000, pp. 283–290.

52. Blomqvist CG, Saltin B. Cardiovascular adaptations to physical training. *Ann Rev Physiol* 1983; 45:169–189.
53. Holloszy JO, Coyle EF. Adaptations of skeletal muscle to endurance exercise and their metabolic consequences. *J Appl Physiol* 1984; 56:831.
54. Holloszy JO. Metabolic consequences of endurance exercise training. In: Horton ES, Terjung RL, eds. *Exercise, nutrition, and energy metabolism*. New York: Macmillan, 1988, pp. 116–131.
55. Womack CJ, Sieminski DJ, Katzell LI, et al. Improved walking economy in patients with peripheral arterial occlusive disease. *Med Sci Sports Exerc* 1997; 29:1286.
56. Albert C, Mittelman M, Chae C, et al. Triggering of sudden death from cardiac causes by vigorous exertion. *New Engl J Med* 2000; 343:1355–1361.

12 Endovascular Strategies for Management of Claudication and Lower Extremity Arterial Disease

*Michael C. Brunner, MD, FSIR, FACR and
Dennis G. Caralis, MD, PhD, MPH, FAHA*

CONTENTS

INTRODUCTION
PERCUTANEOUS TRANSLUMINAL ANGIOPLAST
FOR CLAUDICATION
ATHERECTOMY AND COMPLICATIONS OF ANGIOPLASTY
THE USE OF INTRAVASCULAR STENTS
THROMBOLYSIS
CONCLUSION
REFERENCES

INTRODUCTION

In 1964, Dotter and Judkins introduced therapeutic percutaneous angioplasty of atherosclerotic peripheral plaques, a technique that used multiple coaxial catheters of various sizes to dilate the stenosis. In the mid-1970s, Andreas Gruentzig, at the University of Zurich, Switzerland, developed a double-lumen balloon catheter—used to dilate lesions in the iliac and femoral arteries safely and with a high rate of procedural success. The modern era of cardiovascular interventions had begun. Miniaturization of Gruentzig's balloon catheters system led to the first percutaneous transluminal coronary angioplasty in 1977 in Zurich, per-

From: *Clinical Hypertension and Vascular Diseases: Lower Extremity Arterial Disease*
Edited by: D. G. Caralis and G. L. Bakris © Humana Press Inc., Totowa, NJ

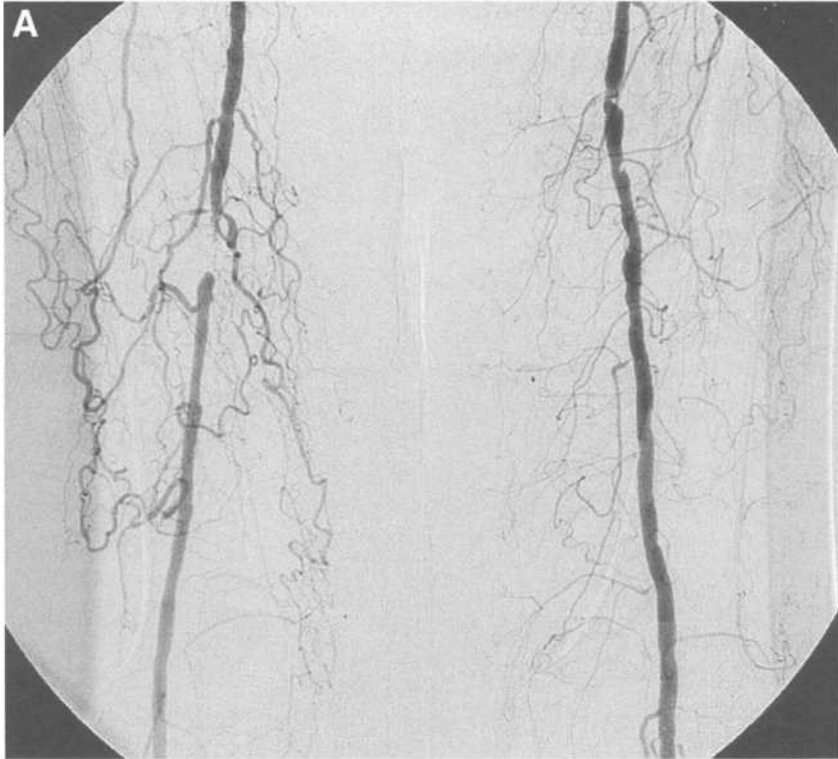


Fig. 1. (A): Pre-intervention angiography. There is significant atherosclerosis of both superficial femoral arteries (SFA) and a discrete 100% stenosis in the distal right SFA. This complete occlusion was felt to be the culprit for the disabling claudication in this 80-year-old woman.

formed by Gruentzig. Since the initial percutaneous interventions, there has been explosive growth in the field of interventional transcatheter therapeutics. This expansion has been fueled by the introduction of an array of new devices, adjuvant pharmacologic therapies, and novel imaging and physiologic measurement catheters designed to overcome some of the limitations of balloon angioplasty. Devices and techniques for lower extremity arterial disease (LEAD) are balloon angioplasty, rotational atherectomy, stents, rheolytic thrombectomy, and distal embolic protection devices. Table 1 lists their indications, potential advantages, limitations, and complications. *See* Fig. 1 for angiography examples.

Whereas, technological breakthroughs of the expandable balloon dramatically improved the initial percutaneous interventional technique of serial dilatation with larger and larger catheters, many attempts have

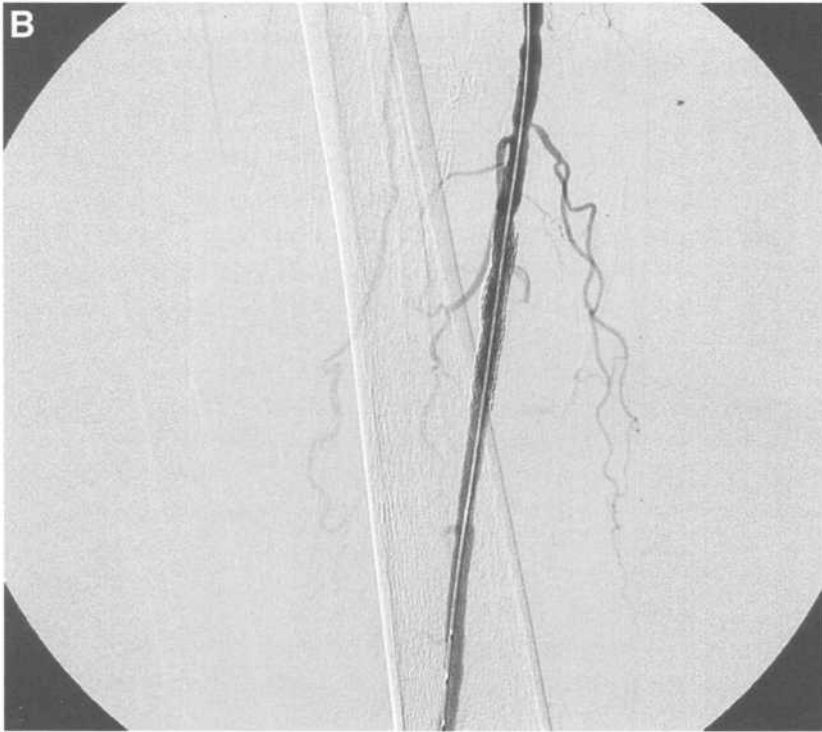


Fig. 1. (continued) (B): Intervention angiography. A balloon angioplasty was performed on the 100% lesion in the right SFA with inadequate results. The lesion was then stented with an excellent angiographic appearance and 10% residual stenosis. The stent, an Exceed 7 × 40 mm self-expanding device, was placed across the lesion.

been made to improve upon or replace this technique. These have included attempts to better control the depth of vessel injury by cutting the plaque with atherectomy catheters, as well as attempts to selectively vaporize the plaque with laser catheters. More recent attempts have been aimed at performing balloon dilation, but controlling the response to injury either by instilling an agent transmurally through the balloon at the site of dilatation in order to modify the body's response to injury or the use of local irradiation to perform a similar function. It has gotten to the point where an acronym *POBA* has been coined to refer to the unmodified technique of *plain old balloon angioplasty*. Many of the innovations touted to be alternatives to *POBA* have been relegated to either obscurity or minor complimentary techniques to improve upon the good results obtained with balloon dilatation. In fact, the major advancements affecting the success rates of endovascular therapy include hydro-

Table 1
Transcatheter Therapies of LEAD

<i>Device/Technique</i>	<i>Indications</i>	<i>Advantages</i>	<i>Limitations, Disadvantages</i>	<i>Complications</i>
Balloon angioplasty Rotational atherectomy	Any noncalcified vascular stenosis Resistant, nonyielding lesions	Simple, easy to use Has a niche in certain lesions; ulcerated eccentric or resistant	Ostial locations, calcified lesions Limited availability for large diameter vessels	Dissection, acute or threatened closure Dissection, distal embolization, no reflow, perforation, increased restenosis
Stents	Most medium and large vessels with eccentric or compliant lesions	Treat dissection and threatened closure, with more predictable outcome in some targets	Limited experience with infrapopliteal arteries	Stent thrombosis, in-stent restenosis may be minimized by drug-eluting stent). Studies needed to be completed for appropriate dosage of larger vessels
Rheolytic thrombectomy	Thrombotic lesions, degenerated vein grafts, peripheral thrombosis or embolus, dialysis access thrombosis	Reduces distal embolization	Can be used primarily in large vessels	Dissection, hemolysis
Cutting balloon	In-stent restenosis, ostial lesions	May be efficacious in resistant plaques	Tortuous arteries	More acute complications (e.g., dissections, perforations)

Brachytherapy	In-stent restenosis	Effective in preventing recurrences	Bulky devices, used primarily in medium and large coronary arteries only; increased radiation exposure, have to coordinate with radiation physicist	Dissection; late thrombosis if new stent is deployed. Long-term effects are unknown
Distal embolic protection devices	Vein graft and carotid interventions, possible use in other peripheral interventions (e.g., renal arteries)	Reduce periprocedural infarction and potentially stroke	Unable to use in large conduits	Ischemia with balloon-occlusion devices
Intravascular ultrasonography (IVUS)	Obtain more anatomical information, evaluate lesion morphology or adequacy of intervention (e.g., stent expansion)	Simple to use	Time-consuming; does not provide physiologic information. Expensive	Need for anticoagulation, dissection

Adapted from Khalil AA, Catheter-based treatment. Postgraduate Medicine 2004;115:16.

philic guide wires and lower profile balloon catheters, which enable the balloon to be more successfully placed at the target lesions.

Therefore, this chapter will focus upon the use of POBA and other intravascular therapeutic interventions above and below the level of the inguinal ligament. Adjunctive techniques to POBA that allow for dilatation of resistant calcified lesions such as atherectomy; or allow for improved balloon dilatation of compliant lesions or treatment of complications of angioplasty such as intravascular metallic stents, and finally therapy to improve the results of balloon dilatation for occlusions with thrombolytic therapy will be discussed.

PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY FOR CLAUDICATION

Angioplasty for claudication can be separated into two anatomic areas for purposes of applicable techniques and expected results. The suprainguinal region describes stenoses in the aortoiliac vessels, whereas the infrainguinal area of pathology includes the femoral and popliteal arteries as well as vessels below the knee.

Aortoiliac angioplasty (with or without stenting) is competitive to aortic bifurcation bypass grafting, a well-established, durable, and safe operation without lengthy recovery period. The major determinants for separating patients between surgical disease and percutaneous transluminal angioplasty (PTA), aside from surgical candidacy, are expected short- and long-term patency results. A joint committee consisting of several councils of the American Heart Association prepared "Guidelines for Peripheral Percutaneous Transluminal Angioplasty of the Abdominal Aorta and Lower Extremity Vessels" which attempts to separate lesions more amenable to angioplasty from those more suitable for a surgical approach. Their conclusions demonstrated that noncalcified, more focal nonostial stenoses are most favorably treated by balloon dilatation. This would also presume the absence of other indications for surgical approach, such as associated aneurysmal disease.

Focal stenotic disease of the abdominal aorta is generally seen in young female cigaret smokers with thigh, hip, and buttock claudication predominant over calf claudication. When present in males it commonly is associated with impotence (Leriche syndrome often associated with aortoiliac disease). Although initially treated as long as three decades ago with a *kissing balloontechnique* from a bilateral transfemoral approach, the development of larger diameter, higher-pressure balloons has made a single transfemoral approach possible with satisfactory patency rates (1).

More extensive data is available for lesions involving the iliac arteries with or without concomitant disease of the distal abdominal aorta. Whereas comparison between different studies is very difficult because of patient selection and exclusion criteria, the technical success rate for iliac stenoses in most series is greater than 90% with the more favorable lesions approaching 100%. Tegtmeier et al. (3) obtained a 79% overall patency, and 85% patency of those procedures initially successful when 200 patients with aortoiliac disease were followed for an average of 29 months mean follow-up. The complication rate was just over 10% (2). Whereas there is a wide body of literature concerning outcome of iliac angioplasty, comparison of success rates in the same patients can vary by as much as 30% when different criteria for evaluating the success of the intervention are utilized (3). The long-term data do not reflect more recent procedures that improve the initial technical and clinical success rate, such as thrombolytic therapy for cases of occlusion and/or intravascular stents for occlusions or suboptimal results after initial angioplasty.

The percutaneous approach to infrainguinal arterial disease is much like that of the aortoiliac region, but with diminished longevity like its surgical counterpart. Similar to the surgical tenant of trying to stay above the knee in therapy for intermittent claudication, the percutaneous approach is primarily guided towards short stenoses of the superficial femoral and popliteal arteries above the knee with an infrageniculate approach primarily reserved for patients with debilitating claudication and/or symptoms at rest.

Although studies vary greatly (3), particularly in whether or not they exclude technical failures from their long term follow-up, most series that select patients with good run off (which should include most patients who suffer from intermittent claudication) have 5-year patencies of approximately 50 to 60% with somewhat worse results for occlusions instead of stenoses, and long length of diseased segment (4,5). The American Heart Association Committee again classified lesions that are most favorable for angioplasty to be single nonostial stenoses less than 3 cm in length that are not heavily calcified and above the knee. Lesions approaching 10 cm in length (including occlusions) with runoff disease of increasing severity are more appropriate for surgical therapy (6). Similar findings have been suggested in cost-effectiveness analyses (7).

Whereas the initial success rates of femoral popliteal angioplasty is currently in the 90% range for stenoses and 80% range for occlusions, much of the recent improvement is again a result of the presence of hydrophilic guide wires, digital subtraction angiography with road mapping, the increased availability of antispasmodic pharmacological

agents, and lower profile catheters and balloon catheters (8). Although perhaps beneficial from a marketing standpoint, the use of lasers in an attempt to improve long-term results over POBA has been unsuccessful (9,10).

ATHERECTOMY AND COMPLICATIONS OF ANGIOPLASTY

Although it was initially hoped that directional atherectomy would demonstrate a lower degree of restenosis as has been suggested in some coronary interventional data, long-term follow-up results of femoral or popliteal directional atherectomy has demonstrated disappointing results compared to POBA (11,12). So that in general, directional atherectomy is reserved for therapy of lesions resistant to balloon dilatation at safe inflation pressures, for treatment of either eccentric lesions or complications of angioplasty such as dissection.

Complications of angioplasty are generally related to the catheter size and location of the puncture site, severity of the patient's disease, and associated comorbid conditions such as hypertension or a need for anticoagulation or thrombolysis. The major complications are all in the order of 2 to 5% and include puncture site hematomas and/or subsequent pseudoaneurysms, intimal dissection (which may, depending upon its severity, be a normal sequela of balloon dilatation rather than a complication), arterial rupture, and distal embolization (13,14,15).

THE USE OF INTRAVASCULAR STENTS

The first bare metal stent approved for peripheral arterial use in the United States by the US Food and Drug Administration is the Palmaz Balloon-Expandable Intraluminal Stent (Johnson & Johnson International Systems, Warren, NJ). It was initially approved for use in the iliac artery after suboptimal results following POBA. The use of this stent has been effective in reducing residual gradient across lesions following iliac angioplasty that may have been caused by either recoil of the vascular wall or flow limiting intimal dissections. Long-term studies indicate that iliac artery stenting provides better long-term patency than angioplasty alone in prospective randomized trials of iliac artery primary stent placement vs POBA (16).

Flexible, self-expanding metallic stents have been used in scientific studies for suboptimal iliac artery results with balloon dilatation and in treating complete occlusions. These stents have the advantage of being more flexible for use in either tortuous arteries or from the contralateral

femoral approach but, may have somewhat less exact placement positioning characteristics compared to balloon expansion delivery systems.

Metallic stenting has significantly less restenosis rate compared to balloon angioplasty for lower extremity arteries. Leading examples of impressive, long-term patency are the stents deployed in the iliac artery. Whereas early PTA failures in infrafemoral sites can often be salvaged by the use of a bare metallic stent, the long-term results have been plagued by intimal hyperplasia and stent occlusion. Although no large prospective, methodologically impeccable randomized study is available, it appeared until recently that short-term patencies are similar to those of PTA alone.

The introduction of drug-eluting stents, Sirolimus-Eluting, may solve the problem of in-stent restenosis in LEAD (17); a gratifying experience similar to that with drug (rapamycin or taxol) eluting stents for coronary lesions.

Stents (17) that allow elution of antiproliferative medications have been developed and are proven to reduce in-stent restenosis to nearly negligible rates (4 to 9% in some trials). The first drug-eluting stent is approved for the US market: the Cypher stent has a polymer coating that elutes sirolimus (Rapamune) during a 2-week period with few or no systemic effects. More stents with different drug coatings will soon be available for high grade stenosis of the arteries of the lower extremities.

Drug-eluting stents are a very promising advance. They could be the answer for lesions at increased risk of restenosis as predicted by smaller vessels, longer lesions, and the presence of diabetes mellitus. Like any new technology, however, this advance raises many unanswered questions. Drug-eluting stents have not been adequately and long term evaluated in LEAD or vein graft lesions.

Biodegradable stents are the products of another technological advancement. A potential advantage of biodegradable stents is that they leave a larger potential surgical target.

THROMBOLYSIS

Selective arterial thrombolysis is usually utilized in the setting of acute limb jeopardy. However, acute or subacute onset of claudication can be treated with thrombolytic therapy. In addition, chronic occlusions, particularly in the iliac artery, can sometimes be better recanalized with the adjunctive use of thrombolytic therapy allowing the placement of a balloon catheter and subsequent intravascular stent.

For claudication resulting from either thrombotic or embolic occlusions, urokinase has been extensively utilized over the past two-and-a-

half decades. The choice of urokinase over other thrombolytic agents, stems from studies asserting its higher efficacy to complication rates when used in the peripheral arterial system. In general, thrombotic occlusions respond much better than emboli to regional thrombolysis. The therapy is rarely effective if a guidewire cannot transverse the occlusion, and the results are most efficacious when a multiside holed catheter can be placed to infuse the agent directly into the thrombus. If successful, thrombolytic therapy can demonstrate a short stenosis that usually underlies an occlusion for thrombotic disease or completely lyse an embolus, if it is fresh enough to respond. In the case of chronic occlusions (especially in the iliac region) an infusion of urokinase may allow recanalization of a channel through which further intervention can be performed. Whereas thrombolytic therapy may not always allow for successful treatment of the underlying disease by percutaneous means, it can often reduce the extent of surgical intervention and will rarely compromise such procedures.

There are three absolute contraindications to the initiation of thrombolytic therapy: (1) active uncontrollable hemorrhage, (2) likely persistent proximal source of embolization, or (3) neurovascular compromise in the affected extremity, where it is likely that a reperfusion injury such as myonecrosis may develop. Relative contraindications include recent intra-abdominal or intrathoracic surgery, uncontrollable hypertension, a recent intracerebral event that is likely to be hemorrhagic, and possibly the recent use of a porous intra-arterial graft material. Thrombolytic complications are proportional to the duration of therapy and usually consist of hemorrhage, often related to concomitant need for anticoagulation.

CONCLUSION

Indeed, there have been advances in techniques allowing for more bare metal stents and drug-eluting stents and occlusions to be crossed by the angioplasty balloon, thereby increasing the initial success rate. Few techniques have improved upon the long-term durability of POBA. The long-term success rate for angioplasty in the iliac region remains in the upper 80% to lower 90%, 60 to 70% patency in the femoral popliteal region, and approximately 50% below the knee. Most of the interventions, including these to help support angioplasty, do not make a subsequent surgical repair more difficult. Hopefully, with advancements already made in controlling intimal hyperplasia by deploying drug-eluting stents, long-term results of angioplasty will continue to improve in a dramatic way. Any revascularization procedure, mechanical or surgi-

cal, should be followed by medical therapy for life to control risk factors for atherosclerosis and potentially reverse its process.

REFERENCES

1. Yakes WF, Kumpe DA, Brown SB, Parker SH, Lattes RG, Cook PS, et al. Percutaneous transluminal aortic angioplasty: techniques and results. *Radiology* 1989; 572:965–970.
2. Tegtmeier CJ, Harwell GD, Selby JB, Robertson R Jr, Kron IL, Tribble CJ. Results in complications of angioplasty in aortoiliac disease. *Circulation* 1991; 83 : 153–160.
3. Rutherford RB, Becker GJ. Standards for evaluating and reporting the results of surgical and percutaneous therapy for peripheral arterial disease. *JVIR* 1991; 83:169–174.
4. Capek P, McLean GK, Berkowitz HD. Femoral popliteal angioplasty: factors influencing long term success. *Circulation* 1991;83:I-70–I-80.
5. Johnston KW. Femoral and popliteal arteries: re-analysis of results of balloon angioplasty. *Radiology* 1992;193:767–771.
6. Pentecost MJ, Criqui MH, Dorros G, et. al. Guidelines for peripheral percutaneous transluminal angioplasty of the abdominal aorta and lower extremity vessels. *Circulation* 1994; 89:511–531.
7. Hunink, MGM, Wong JB, Donaldson MC, Meyerovitz MF, deVries J, Harrington DP. Revascularization for remoropopliteal disease: a decision and cost-effectiveness analysis. *JAMA* 1995; 274: 165–171.
8. Becker GJ. Stents for Peripheral Vascular disease, Tuesday, March 28, 1995; presented at the plenary session of the Society of Cardiovascular and Interventional Radiology Scientific Meeting in Fort Lauderdale, FL.
9. Belli AM, Cuberland DC, Proctor AE, et al. Follow-up of conventional angioplasty vs. laser thermal angioplasty for total femoral popliteal artery occlusions: results of a randomized trial. *J VASC Interv Radiol* 1991; 2:485.
10. Huppert PE, Duda SH, Helbert V, et al. Comparison of pulse laser assisted angioplasty and balloon angioplasty in femoral popliteal artery occlusions. *Radiology* 1992; 184:363.
11. Katzen PT, Becker GJ, Benanati JF, et al. Long-term follow-up of directional atherectomy in the femoral and popliteal (abstract). *JVIR* 1992; 3:39.
12. Dorros G, Lyer S, Lewin R, et al. Angiographic follow-up and clinical outcome in 126 patients after percutaneous directional atherectomy for occlusive peripheral vascular disease. *Cathet Vasc Diag* 1992; 22:79.
13. Bergqvist D, Johnsson K, Weibull H. Complications after percutaneous transluminal angioplasty of peripheral and renal arteries. *Radiology* 1987; 28:3–12.
14. Gardiner GA, Meyerovitz MF, Stokes KR, Clouse ME, Harrington DP, Bettmann MA. Complications of transluminal angioplasty. *Radiology* 1986; 159:201–208.
15. Weibull H, Bergqvist D, Johnsson K, Karlsson S, Takolander R. Complications after percutaneous transluminal angioplasty in the iliac, femoral and popliteal arteries. *J Vasc Surg* 1987; 5:681–686.
16. Richter GM, Roeren TK, Noeldge G, Landwehr P, Lackner KG, Kauffmann GW. Balloon-expandable stent placement vs PTA in the iliac artery stenoses and occlusions: long-term results of a randomized trial (abstract). *J Vasc Interventional Radiol* 1992; 3:9.
17. Scheinert D, Scheinert S, Schmidt A, Braunlich S, Muniez-Devos D. Sirolimus-eluting stents in obstructions of the superficial femoral artery: Long-term results of double-blind randomized trial (Sirocco trial) 2003. *Circulation* 2003; 108: abstract 2753.

13 Severe Lower Extremity Arterial Disease

Limb Salvage and Revascularization

*Chad E. Jacobs, MD
and Walter J. McCarthy, MD*

CONTENTS

INTRODUCTION
SURGICAL INTERVENTION
OPERATIVE OPTIONS
CONDUIT OPTIONS
COMBINED REVASCULARIZATION AND FREE TISSUE
TRANSFER
SYMPATHECTOMY
SUBINTIMAL ANGIOPLASTY
GENE THERAPY
CONCLUSION
REFERENCES

INTRODUCTION

Innovations in surgery, radiology, and medical management during the past 30 years have allowed patients who once faced certain amputation as a result of leg ischemia to be offered a variety of alternatives. Patients with limb-threatening ischemia differ from those with intermittent claudication in regard to both natural history and treatment requirements. Management of patients with claudication involves risk factor modification, exercise regimens, and pharmacologic intervention. This

From: *Clinical Hypertension and Vascular Diseases: Lower Extremity Arterial Disease*
Edited by: D. G. Caralis and G. L. Bakris © Humana Press Inc., Totowa, NJ

group rarely requires amputation. Patients with critical limb ischemia are most often treated surgically in order to preserve limb functionality. Five year rates of limb salvage for this patient population have been shown to be 81% for femoropopliteal bypass and 47% for infrapopliteal bypass (1). However, despite continued additions to our treatment armamentarium, it has been shown that amputation rates have remained the same over the past decade (2). The mortality from major amputations is generally reported to be 3 to 10% (3), but in selected populations, such as those over 80 years old, mortality may be as high as 82% (4). In addition, the rehabilitation outcome after amputation for nonreconstructible arterial disease is usually overestimated. One recent study (5) reported that only 26% of patients were able to ambulate outdoors with a prosthesis 2 years after major amputation. Another study predicted that the number of amputations performed in the geriatric population will double by the year 2030 (6). The implications for future health resource allocation are somewhat daunting once these statistics are reviewed.

Our goal as clinicians in the field of peripheral arterial disease should be to apply the multiple technological advances that we have toward limb salvage and the prevention of amputation. This chapter will discuss the surgical, percutaneous, and medical adjuncts available in this regard.

SURGICAL INTERVENTION

The surgical treatment of lower-extremity ischemia must be based on the severity of the patient's symptoms and the overall medical condition of the individual. Atherosclerosis is a systemic process, and these patients are predisposed to stroke, myocardial infarction, and hypertension caused by the involvement of other arterial segments. The extent of such involvement requires full evaluation prior to lower extremity surgery, and some patients may require carotid endarterectomy or coronary artery bypass grafting or stenting before infrainguinal reconstruction is undertaken.

Indications for surgical revascularization include disabling claudication and limb-threatening ischemia. Patients with moderate symptomatic ischemia present with claudication and are candidates for a reconstructive operation only if this disability severely limits their lifestyle or occupational activity. Most patients who claudicate do not require an operation to prevent limb loss, and several large studies have shown that such patients have only a small risk (approximately 5%) of requiring a major amputation within five years of onset of symptoms (7,8). Therefore, most patients who present with intermittent claudication are managed nonsurgically. Such treatment includes formal exer-

cise programs, smoking cessation, risk factor management, and pharmacological interventions as discussed elsewhere in this text.

Interventions for limb salvage are required if a patient develops rest pain, nonhealing ulcers, or gangrene of the toes or foot. After appropriate treatment, rest pain disappears, ulcers heal with standard attention, and gangrenous tissue can be amputated with prompt healing. This allows substitution of a minor toe or forefoot amputation for an otherwise inevitable below- or above-knee amputation. All effort is made to preserve as much extremity as possible so that the potential for rehabilitation is optimal.

OPERATIVE OPTIONS

Selecting the appropriate procedure comes after careful patient evaluation including medical history, physical examination, noninvasive testing, and arteriography. Because there is often arterial disease in several areas, it is essential to determine the arterial segment with the most hemodynamically significant stenosis. The occlusion may be proximally at the aortoiliac level, thus affecting inflow to the lower extremity. It is a fundamental principle that inflow should be restored prior to correcting outflow lesions to the foot. This prevents a newly placed bypass graft from thrombosing as a result of inadequate blood flow through the graft.

If in fact the aortoiliac segment is diseased, an aortofemoral bypass graft may alleviate the patient's symptoms. Patients who cannot tolerate an abdominal operation may undergo axillofemoral reconstruction, supplying the lower extremities with blood flow from an axillary artery through a graft tunneled in the subcutaneous tissue. However, the distinct disadvantage of axillofemoral reconstruction is the much shorter patency rate when compared with the traditional aortobifemoral bypass graft (9). If a patient has adequate blood flow to the contralateral leg, a femoral-femoral bypass graft can be used to provide sufficient inflow. Percutaneous angioplasty and stent placement are also common techniques used in the management of iliac artery occlusive disease, and will be discussed in greater detail later.

Once it has been ascertained that inflow to the level of the femoral arteries is adequate, infrainguinal reconstruction can be undertaken. The two traditional approaches for correcting arterial occlusion are either to open the artery and remove the obstruction by endarterectomy, or to fashion a bypass around the obstruction. Longstanding experience has established direct bypass of obstruction as the dominant and superior technique. However, endarterectomy is still used as an adjunct to bypass grafting, and even sometimes alone, such as in the case of a profundoplasty to repair a stenotic profunda femoris artery.

Determining the most appropriate bypass procedure involves identifying the exact level of occlusion, the best proximal site for inflow, and the best distal site for outflow. The proximal anastomosis may be sewn to the common femoral artery, the profunda femoris artery, the superficial femoral artery, the popliteal artery, or even the limb of an aortobifemoral or femorofemoral bypass graft. The distal end of the graft is anastomosed to the most cephalad portion of the leg that allows unobstructed blood flow to the foot. The most common point of arterial occlusion in the lower extremity is at the inferior portion of the superficial femoral artery as it courses through the medial adductor muscles just above the knee, a location known as Hunter's canal. A femoral-popliteal bypass graft is therefore one of the most frequently performed arterial reconstructions. If the above-knee popliteal segment is diseased, the graft can simply be anastomosed to the below-knee segment of the popliteal artery.

In the event that there are no tibial branches remaining in continuity with the popliteal artery, the graft may be anastomosed directly to any one of the three tibial arteries. Because of technique, body habitus, and image quality the tibial vessels may be difficult to adequately visualize on preoperative angiogram. In such cases, an intraoperative arteriogram performed immediately prior to bypass can be quite helpful in determining adequacy of distal target vessels. The tibial vessel with largest diameter, least amount of occlusive disease, and best runoff to the foot should be selected for the distal anastomosis. After completion of the bypass procedure, a completion arteriogram should be performed in the operating room to inspect the reconstruction. If technical flaws are discovered, they can be repaired while the patient is still anesthetized and the graft and anastomosis are still exposed.

CONDUIT OPTIONS

Autogenous Vein

The long-term success of bypass grafts performed below the inguinal ligament depends largely on the type of conduit utilized. Despite general agreement that autogenous saphenous vein provides the best long-term success for distal lower extremity bypass, there is some controversy regarding the optimal technique for constructing such bypasses. The two most widely used techniques include reversal of the saphenous vein and the *in situ* technique. Each technique has inherent advantages. The reversed technique must be used if a patient has inadequate or previously harvested saphenous vein in the ipsilateral extremity. Furthermore, use

of a reversed segment does not require valve lysis as is necessary for *in situ* use. One of the disadvantages of the reversed technique is the size mismatch that is necessitated when the distal, smaller end of the vein is anastomosed to the proximal, larger artery. Similarly, the larger proximal vein must be anastomosed to the smaller, distal artery. Despite these apparent shortcomings, the reversed saphenous vein technique is one of the most commonly used and most successful bypasses performed. Reported patency rates for infrainguinal reversed saphenous bypass grafts are between 75 and 80% at 5 years with a limb salvage rate of 90% (10–12).

The *in situ* technique, first described by May et al. (13), eliminates the concern of anastomotic size mismatch. Use of the *in situ* technique has the theoretical advantage of preserved endothelial function resulting from an intact vaso vasora as well as improved graft hemodynamics, but to date this has not been supported by conclusive data from laboratory studies. Important principles for *in situ* use include valve lysis and ligation of side branches to prevent arteriovenous fistulae. Valve lysis is usually performed after creation of the proximal anastomosis, so that arterial pressure distends the vein to the level of the most proximal valve. A valvulotome is then introduced into the vein through either a side branch or the distal most end and is passed through the valves to cause their lysis. Valves are disrupted in a systemic fashion so that pulsatile uninterrupted blood flow is established through the entire vein graft. Whereas the majority of the *in situ* bypass graft remains undissected in the subcutaneous tissue, the distal end must be dissected and mobilized in order to perform the distal anastomosis. Once this has been completed, side branches must be ligated to prevent arterial blood from entering the venous circulation. Side branch points may be identified by Doppler ultrasound, by small incisions and direct visualization, or by angioscopy, in which case the branches may be not only identified but coil embolized as well. Patency rates for the *in situ* saphenous vein technique have been reported as 65 to 85% with a limb salvage rate of 82% (12,14–16).

Unfortunately, autologous saphenous vein may not always be of sufficient length or diameter for the contemplated procedure, or it may have been harvested for use in another procedure. Alternative autologous vein may be obtained from several locations, including the lesser saphenous vein, the superficial femoral vein, and upper extremity veins. A common approach is to utilize arm vein grafts as the next alternative when saphenous vein cannot be used. In preparation for using arm veins as a conduit, preoperative ultrasound vein mapping can be useful in identifying the location, patency, and diameter of veins. Some surgeons use angioscopy

as well to identify webs, bands, or other sequelae of pre-existing injury to arm veins as a result of venipuncture or cannulation. However, the results of arterial reconstruction with arm vein grafts are not as encouraging as those with saphenous vein grafts. In a recent large study (17), evaluating arm vein as a conduit for arterial bypass, the 3-year primary patency rate was 52%, the 3-year secondary patency rate was 60%, and limb salvage was 80%.

Synthetic Conduits

Synthetic conduits are another option for limb salvage in patients requiring arterial reconstruction as a result of severe atherosclerotic occlusive disease. Despite many clinical studies, the role, indications, and optimal use of synthetic conduits in lower-extremity bypass continue to be a controversial topic. The synthetic graft most widely used today is expanded polytetrafluoroethylene (ePTFE). Initially used industrially as a wire insulator, ePTFE was first used in humans as a vascular conduit in 1976 (18). Polyethylene terephthalate (Dacron) is another synthetic fabric that can be woven or knitted into a bypass conduit. Dacron grafts are sometimes used for lower extremity arterial reconstruction today, and are used frequently by many surgeons for aortic reconstruction. Demonstrating a renewed interest in the use of Dacron for lower extremity bypass, a recent study compared ePTFE vs Dacron for above-knee femoropopliteal bypass, and showed no statistically significant difference between the two synthetic graft choices in regard to primary or secondary patency (19). Regarding ePTFE, several studies in the past have shown that in comparison to autologous saphenous vein, when used for above-knee femoropopliteal bypass, 4- and 7-year patency rates are not statistically different between the two conduits (20,21). However, a more recent randomized trial demonstrated that for above-knee bypasses, autogenous vein had a significantly better 5-year patency rate than ePTFE (76% vs 52%) (22). In addition, when used for reconstructions below the knee, ePTFE has been shown to be considerably inferior (20,23).

Because ePTFE grafts have less than optimal results compared to native vein, several techniques have been employed when autologous vein is in short supply and prosthetic graft material must be used for limb salvage. The use of a vein cuff or patch at the distal anastomosis improves the patency of ePTFE grafts in below-knee vessels (24,25). This may be caused by a reduction in compliance mismatch, as well as alteration in the shear stress flow patterns at the distal anastomosis (26,27). A recent large study (28) found that such composite grafts had a 5-year primary patency of 58%, 5-year secondary patency of 75%, and limb salvage rate

of 80%. These results are clearly superior to infrageniculate bypass using ePTFE alone.

Another alternative in certain situations is the use of a composite-sequential bypass. This technique may be applied if a patient has occlusive disease requiring bypass both above and below the knee (i.e., superficial femoral and trifurcation disease), but has a patent isolated popliteal segment. Under these circumstances, a prosthetic bypass can be performed down to the popliteal segment, and an autogenous vein graft is then placed between either the prosthetic or the native popliteal artery and the distal infrageniculate outflow vessel. This technique was designed to avoid the poor patency rates that accompany an infrageniculate bypass using ePTFE. Published data with this reconstructive technique reveal a 1-year patency and limb salvage rate of 80% and 88%, and a 4-year patency and limb salvage rate of 40% and 70% (29,30).

Allografts

In 1975, Dardik (31) introduced the human umbilical vein for use as a bypass graft, and since that time surgeons have acquired a relatively large experience with this conduit. The umbilical vein is fixed in gluteraldehyde, which enhances crosslinking of collagen at the molecular level and theoretically results in a stronger graft. The gluteraldehyde also destroys the endothelium and minimizes the immunogenicity of the graft. Once the human umbilical vein is fixed, it is not viable and is essentially a musculocutaneous tube. One disadvantage of human umbilical vein when compared to ePTFE is the greater difficulty of handling, tunneling, and anastomosing the graft. The graft tissue is fragile, friable, and does not tolerate traction. If not handled appropriately in the course of rinsing off the tanning agent and tunneling during the procedure, the umbilical vein is prone to develop mural dissection. Suturing the graft may be difficult owing to the thickness of the graft and the necessity of incorporating not only the vein but the polyester wrap as well. After early animal studies demonstrated a significant incidence of human umbilical vein graft dilatation (32), manufacturers added a Dacron mesh around the graft to prevent dilatation and aneurysm formation.

In terms of graft patency, a large prospective randomized Veterans Affairs Cooperative study (33) compared human umbilical vein with ePTFE and autogenous saphenous vein for lower extremity bypass. For patients in whom a bypass was performed for limb salvage (critical ischemia), 5-year cumulative assisted primary patency rates for human umbilical vein were 53%, which was better than the ePTFE rate of 37%

but not as good as the saphenous vein patency rate of 68%. However, the rate of perioperative (30 day) graft thrombosis was significantly higher in the umbilical vein group (12.2%) compared to the ePTFE group (2.2%). Interestingly, the rate of limb salvage was significantly higher for patients who received umbilical vein graft (90.4%) vs ePTFE (87.5%).

Despite the addition of the Dacron mesh wrap, the nemesis of the human umbilical vein graft continues to be dilatation and aneurysm formation. Aneurysm formation in the human umbilical vein graft is most likely a consequence of biodegradation, and most studies have found that clinically apparent aneurysm formation occurs an average of five years after graft implantation. These studies have shown the incidence of aneurysm formation to be between 33% and 57% (34–36), but reoperation is only required in 0.04 to 3.3% of cases (33,37). Aneurysmal rupture has been an extremely infrequent event (33). Nonetheless, the combination of technical difficulty when dealing with the graft material, relatively high rates of early graft thrombosis, and increased aneurysmal degeneration has made the human umbilical vein graft a complicated graft with which to work.

Fresh nonfixed arterial conduit is a form of allograft that can be used as a transplant in the absence of adequate autogenous vein. An intact endothelial lining is important for improved long-term patency in distal bypass grafts (38–40) and this can only be provided with fresh grafts implanted immediately after harvest. Tissue preservatives such as gluteraldehyde and dialdehyde starch may predispose to graft thrombosis or biodegradation leading to aneurysm formation. The concept of providing a fresh arterial graft with intact endothelium was tested in a study using arterial allografts harvested from brain-dead donors. The data demonstrated that with low dose immunosuppression, a limb salvage rate of 75% at 1 year could be achieved (41).

With the advent of cryopreservation techniques, it is now possible to preserve the arterial endothelium and smooth muscle cells and their properties of contractility and vessel wall relaxation (42,43). A large retrospective multicenter study examined a population in which either fresh or cryopreserved arterial allograft was used for limb salvage infrainguinal reconstruction. The data from this report demonstrated suboptimal 5-year primary and secondary patency rates of 16% and 26%, but a respectable 74% 5-year rate of limb salvage (44). While it does have drawbacks, the use of arterial allograft, either fresh or cryopreserved, represents another available conduit with which to allow reconstruction for limb salvage.

COMBINED REVASCULARIZATION AND FREE TISSUE TRANSFER

Sometimes a patient may have suitable size and length of autogenous vein for a lower extremity bypass, but the appropriate distal target vessel is in close proximity to nonviable tissue or exposed tendon or bone. Extensive tissue loss, proximal foot osteomyelitis, or joint involvement sometimes leaves patients with little recourse other than amputation. These patients often have wounds that would not heal, even with normalized arterial circulation and partial foot amputation. A viable alternative in such cases would be revascularization with free tissue transfer. A number of tissue coverage flaps, including omentum, rectus abdominis, latissimus dorsi, temporalis, gracilis, scapular, and radial forearm flaps can be surgically mobilized and a vascular pedicle preserved. The distal bypass is then performed, the free flap is surgically revascularized from the graft, and adequate coverage and healthy tissue are thus provided for wound healing. The transferred tissue flap not only provides wound coverage, but also increases the flow through the newly constructed graft and may increase its patency (45). A recent study (46) using this technique of combined arterial reconstruction and free tissue transfer demonstrated an 86% limb salvage rate in this desperate patient population. Clearly, this technique represents an extension of our ability to achieve reliable limb salvage in patients with severe leg ischemia.

SYMPATHECTOMY

In 1913, Leriche and Jaboulay (47) first described and tested the concept of sympathetic denervation as therapy for ischemia secondary to arterial occlusive disease. Despite less than optimal initial results, others soon applied the technique with better long-term results, and by the mid-1920s, sympathectomy had emerged as the only alternative to amputation for severe arterial occlusive disease. By the early 1960s, advances in pain control and arterial reconstruction combined with considerable debate over the true value of sympathectomy led to a substantial decline in its use. Today, sympathectomy remains a well-described technique with a diminishing number of applications.

The sympathetic nervous system helps regulate heat loss by providing resting tone to cutaneous arteriovenous anastomoses. These anastomoses are large diameter (50 μm) arteriovenous shunts that bypass nutrient capillary beds and typically do not supply subcutaneous tissue or muscle. An increase in sympathetic outflow results in less blood flow through these cutaneous anastomoses, as well as piloerection and sweat-

ing. Sympathectomy, therefore, results in unopposed parasympathetic stimulation and results in a net increase in blood flow to an ischemic limb. Cronenwett, using radiolabeled microspheres in a canine model, demonstrated that after sympathectomy there was an eightfold increase in total extremity blood flow, which was directly a result of increased flow through the cutaneous arteriovenous (AV) anastomoses (48). Only a modest change in muscle perfusion, either at rest or upon exertion, was identified (49). Vasodilatation and increased net limb perfusion are seen immediately after sympathectomy, but begin to decrease at one week and are diminished almost to baseline levels by 6 months (50). This may be related to either nerve fiber regeneration or development of hypersensitivity to circulating catecholamines.

Despite experimental evidence that muscular perfusion is not significantly enhanced with sympathectomy, there is clinical evidence that certain patient populations may benefit from sympathectomy. Up to 80% of patients with an ankle-brachial index of greater than 0.30, no known neuropathy, and limited tissue loss may obtain relief of their symptoms with sympathectomy (51). Yao and Bergan (52) demonstrated the presence of a threshold in regard to arterial inflow by showing that in 90% of limbs with an ankle-brachial index of less than 0.30, no response was obtained with sympathectomy. An ankle-brachial index of 0.30 may therefore represent a marginal level of perfusion that may suffice to achieve limb salvage if slightly improved by sympathectomy (53).

Unfortunately, there have been no randomized controlled studies to date that evaluate the efficacy of sympathectomy in treating advanced arterial occlusive disease. There have been several uncontrolled studies (51,54-57) that demonstrate relief of rest pain and healing of ischemic ulcers in 28 to 73% of patients and acute limb salvage rates of 60 to 94%. The wide range of these results and lack of a randomized and controlled setting brings into question the effect of placebo as well concomitant medical therapies and conditions.

In treating limb-threatening ischemia, sympathectomy has a limited role because arterial construction is more reliable and yields a far greater chance of limb salvage. Patients who are candidates for sympathectomy are truly nonreconstructible and have at least some inflow (as manifested by an ankle-brachial index greater than 0.30), no evidence of neuropathy, and limited tissue loss. Response to preoperative chemical sympathetic blockade may predict success for operative sympathectomy. In carefully selected patients, sympathectomy may provide the small increase in limb perfusion needed to tip the scales in the direction of ulcer healing and resolution of rest pain.

Percutaneous Intervention

Percutaneous intervention is now an accepted technique for management of patients with severe lower extremity arterial occlusive disease. The two most common forms of percutaneous treatment involve arterial dilatation via balloon angioplasty and intravascular stent placement. Arterial dilatation is achieved by passing a catheter-mounted balloon over an angiographic guidewire through the offending lesion. Arterial access is typically obtained at a site remote from the lesion so as to allow maximum maneuverability. Once the lesion is crossed with a balloon that has been sized at or slightly greater than the size of the native vessel, the balloon is inflated to six to eight atmospheres of pressure and kept inflated for one to two minutes. Effacement of any waist or indentation in the balloon indicates successful angioplasty of the lesion. Balloon inflation in an area of stenosis causes plaque fracture and stretches the media and adventitia of the vessel, thereby enlarging its diameter. The balloon is then deflated and an arteriogram is performed to assess for residual stenosis, dissection, spasm, or recoil. Repeat balloon dilatation, stent placement, or administration of spasmolytic agents can then be performed if any of these conditions exist. In addition, pre- and post-intervention intra-arterial pressure measurements across a lesion can be obtained to determine not only the degree of significance of a stenosis, but to assess the adequacy of treatment as well.

In 1987, Johnston and colleagues (58) published a sentinel report that described 5-year results of a prospective study of percutaneous angioplasty. During an 8-year span, 984 angioplasties were performed in vessels ranging from the aorta to the tibial vessels, with 13.1% of these interventions being performed for limb salvage (rest pain, ulceration, or gangrene). Successful angioplasty was defined as one level of clinical grade improvement as well as either an increase in the ankle-brachial index of 0.10, improvement in Doppler waveform or pulsatility index, or doubling of treadmill exercise distance. The overall initial success rate was 88.6% with a 5-year success rate of 48.2%. However, for patients in whom the indication was limb salvage the initial success rate was 71% with a 5-year success rate of 34%. Further differences were seen depending on location of the angioplasty. In all patients, angioplasty in the common iliac artery had a 5-year success rate of 60% whereas angioplasty in the femoropopliteal segment had a 5-year success rate of 40%. Predictors of success in this study were found to be indication (claudication vs limb salvage), angioplasty site (common iliac vs other), severity of lesion (stenosis vs occlusion), and status of runoff (good vs poor). From this data, the authors predicted that for limb salvage, a

patient with common iliac stenosis and good runoff has a 50% chance of 5-year success after angioplasty. A similar patient with femoropopliteal stenosis would have a 38% chance of 5-year success.

Iliac Angioplasty and Stenting

Because of the early data demonstrating a significant difference in percutaneous results for iliac versus femoropopliteal angioplasty, they are considered to be distinct entities with different management algorithms. Iliac angioplasty has a reported 1-year success rate of 84 to 90%, and a 5-year success rate of 50 to 72% (59–61).

Introduction of metallic stents has allowed for intravascular placement of devices that augment our percutaneous capabilities. Stents serve as an intravascular scaffold and oppose the elastic recoil of the media and adventitia that often occurs after angioplasty. They can also radially compress a fractured plaque that is often the result of forceful dilatation of a stiff or calcified lesion, and in doing so a stent seals off any potential or real dissection planes. Sealing off the arterial media from exposure to circulating blood may limit production of factors that can lead to intimal hyperplasia, thus theoretically improving long-term patency. Arterial stent placement is most commonly indicated after suboptimal angioplasty, and some specific indications include flow-limiting dissection, residual pressure gradient (>15 mmHg), residual stenosis $>30\%$, and failure to establish initial patency. Some controversy surrounds the concept of primary stent placement in the iliac arteries, as will be discussed below.

In 1992, Palmaz and colleagues (62) reported multicenter trial data with use of the Palmaz stent in iliac arteries. Stents in this trial were placed in 496 patients, 156 of which were for limb salvage (32%). The mean pre-stent arterial pressure gradient was 39.1 mmHg, which was reduced to a mean of 1.3 mmHg after stent placement. Immediate success rates were 99.2%, and 43-month success rates were 68.6%. Note that this data includes both claudicants and patients with severe limb-threatening ischemia. Other studies using combined populations have shown similar data, demonstrating a 2-year success rate of 71% using Wallstents (63) and 5-year success rates of 79% using Strecker stents (64).

Given the variable ranges of success among different reports examining iliac angioplasty and stent placement, Bosch and Hunink (65) in 1997 performed a meta-analysis comparing these two treatment modalities. When data from six angioplasty studies and eight stent studies were combined, analysis suggested superiority of stenting for iliac lesions. In patients with critical ischemia, 4-year primary patency rates for

Table 1
Four-Year Primary Patency Rates for Limb Salvage Patients (65)

	Iliac stenosis	Iliac occlusion
Angioplasty	53%	44%
Stent	67%	53%

angioplasty were 53% for iliac stenoses and 44% for iliac occlusions that were treated. With stent placement, the same patient population had 4-year primary patency rates of 67% for iliac stenoses and 53% for iliac occlusions (Table 1). There was no statistically significant difference in complication or mortality rates with either approach.

Results such as these have ignited a controversy over whether the percutaneous management of iliac lesions should involve primary stent placement, i.e., stent placement regardless of angioplasty outcome. The only prospective randomized data to date comparing primary stent placement to angioplasty has been reported in abstract form by Richter and colleagues (66,67). The updated abstract in 1993 described 123 patients who received stents and 124 patients who underwent angioplasty alone. Cumulative 5-year angiographic patency rates in the stent group were 93.6% compared to 64.6% in the angioplasty group. Early success, late success, and patency rates were all significantly better in the stent group. Although these early results seem to favor primary stent placement for iliac occlusive disease, published data in a prospective randomized fashion is lacking and further studies are needed before the question can be definitively answered. It is clear, however, that percutaneous management of iliac artery occlusive disease, be it via angioplasty alone, angioplasty and stenting, or primary stenting, is another important tool to assist us in salvaging limbs in patients with limb-threatening ischemia.

Infrainguinal Angioplasty and Stenting

In 1992, Johnston and colleagues (68) published re-analyzed data regarding angioplasty of the femoral and popliteal arteries. Of a total of 254 patients, 50 (19.7%) underwent femoropopliteal angioplasty with the intent of limb salvage for critical limb ischemia. Whereas the overall 5-year success rate was 38.1%, the 5-year success rate in the limb salvage population was closer to 30%. This echoed the authors' previous findings that angioplasties performed for claudication generally fared better long-term than those done for limb salvage. Other variables found to be predictive of long-term success included severity of lesion (stenosis vs occlusion), quality of runoff, and initial ankle-brachial index of

greater than 0.57. This is in general agreement with the findings of other authors, with the addition of poorer long-term results with longer lesions, especially those greater than 10 cm. Interestingly, although the 5-year success rate for below-knee angioplasty was lower than that of above-knee angioplasty, this difference did not reach statistical significance. Other studies of infrageniculate angioplasty have reported fairly dismal results, with 3-year success rates of only 20% (69).

Because of the overall discouraging results from studies evaluating short- and long-term infrainguinal angioplasty alone, stents have been employed to attempt to increase success rates in this area. As discussed previously, intravascular stents serve to oppose post-angioplasty elastic recoil as well as to provide the radial scaffolding that compresses fractured plaque and seals dissection planes. A number of studies have evaluated intravascular stent placement for superficial femoral atherosclerosis, and the results are quite variable (63,70–75). These studies, as most others discussed, evaluate a mixed population in which indications include both claudication and limb salvage. The percentage of procedures performed for limb salvage in the above referenced studies ranged from 6 to 50%. One-year primary patency rates ranged from 22 to 81% with an average of 58%, and secondary patency rates at one year ranged from 43 to 96% with an average of 73%.

Gray and colleagues (75) evaluated 55 patients who underwent superficial femoral artery stenting after suboptimal angioplasty. This indication for intervention in this patient group was 50% claudication and 50% limb salvage. Stents were placed after suboptimal angioplasty as defined by flow-limiting dissection, residual pressure gradient of >15 mm Hg, residual stenosis of >30%, or failure to establish initial patency. The mean lesion length in this study was 16.5 cm, which is longer than the lesions treated in the previously referenced articles (3.7–13.5 cm). The authors found a mean increase in ankle-brachial index of 0.23, a 1-year primary patency rate of 22%, and a 1-year secondary patency rate of 46%. In the patients treated because of critical limb-threatening ischemia, amputation was eventually performed in 5 of 29 patients, yielding a limb salvage rate of 83%. Lesion length, occlusion versus stenosis, number and type of stent, presence of diabetes mellitus, preprocedural ankle-brachial index, and smoking status were all found to be not statistically significant factors in predicting success for infrainguinal stent placement.

Reviewing the available data, several guidelines can be recommended regarding infrainguinal angioplasty and stent placement for limb salvage in patients with lower extremity arterial occlusive disease. Initial

success with angioplasty is more likely if a stenosis rather than an occlusion is being treated, whereas late success is more dependent on adequate runoff. Length of lesion appears to inversely correlate with successful percutaneous intervention, either angioplasty or stent placement. In contrast to the iliac system, there is no data to support the notion of primary stenting in the infrainguinal vessels. Rather, stents in this setting should be used as an adjunct to suboptimal angioplasty results or recurrent stenoses after angioplasty. Whereas surgical revascularization remains the treatment of choice, for patients without adequate conduit or for those who are a prohibitive surgical risk, angioplasty and stenting are techniques that can help provide limb salvage.

SUBINTIMAL ANGIOPLASTY

Subintimal angioplasty is a technique that has shown some promise in treating patients with limb-threatening ischemia that have complete infrainguinal vessel occlusion and long-segment disease, two distinct factors that have been shown to correlate with poor results when treated with standard angioplasty. In 1990, Bolia and colleagues (76) first reported the technique of subintimal angioplasty. Unintentional dissection of the arterial wall occurs not uncommonly and is usually without sequelae, but until recently was considered an indication to abandon further attempts at angioplasty. Bolia observed that a successful outcome could be achieved if the accidentally created subintimal false lumen was pursued, with re-entry in to the true lumen beyond the distal extent of the occlusion. Thus, the concept of deliberate subintimal angioplasty was born.

Several studies have evaluated subintimal angioplasty of the femoropopliteal segment and demonstrated primary technical success rates of 74 to 85%, and hemodynamic patency rates of 59 to 75% at 1 year and 58% at 3 years (77–79) McCarthy and colleagues (79) recently reviewed their experience of 69 subintimal angioplasties, 43 (62%) of which were performed for critical limb ischemia. The procedure was successfully completed in 31 (72%) of these limb-salvage patients, and of those 31 patients, there was a 68% rate of limb salvage and a 79% rate of hemodynamic patency at 6 months.

Others have evaluated the efficacy of subintimal angioplasty in the infrageniculate vessels (80–82). They have shown that this technique can be successfully performed in 78 to 86% of attempted patients, with a 1-year patency ranging from 53 to 56% and limb salvage rates ranging from 81 to 94%. Importantly, technical failure does not preclude con-

ventional revascularization surgery, and complications of this technique may often be corrected with standard endovascular procedures.

Subintimal angioplasty is a technically difficult procedure with a long learning curve. Results are inferior to surgical bypass, and this technique is not widely performed in the United States. Nonetheless, it does represent yet another option for limb salvage in the management of select patients with severe lower extremity occlusive disease.

Nonoperative Nonpharmacological Intervention

HIGH-PRESSURE INTERMITTENT COMPRESSION

The concept of manual compression therapy for arterial insufficiency is an old one, being mentioned as far back as the first volume of *Lancet* in 1835 (83). One of the proposed mechanisms by which compression therapy works is via augmenting the arteriovenous pressure gradient in the lower extremity. The difference between arterial and venous pressure is the driving force behind perfusion. In the legs of normal patients, the large gradient between arterial and venous pressures drives blood out of the arteries, through the muscle beds, and into the venous circulation. In patients with arterial occlusive disease, decreased arterial pressures translate into a lower arteriovenous gradient that results in decreased perfusion. However, in the presence of competent venous valves, if the leg is briefly compressed with an external pressure that exceeds venous pressure, the veins will empty and the venous pressure is reduced by approximately 15 mmHg (84). Until the veins refill, this decreased venous pressure partially restores the arteriovenous gradient and helps favor increased forward flow. The veins refill after about 14 seconds, at which point another compression is needed to continue the increased perfusion (85).

Another proposed mechanism is the release of vasoactive substances by the shear stress that results from mechanical compression of vessel walls. Animal studies have demonstrated increased endothelial-derived relaxing factor (EDRF) production in response to compression of arterial segments (86). Others have shown that short periods of shear-stress application result in an increase in mRNA production for nitric oxide (NO) synthase (87). It has also been shown that the vasodilatation response is attenuated if NO production is halted by the administration of drugs that inhibit NO synthase (88). Other studies show that limb compression leads to systemic vasodilatation in a manner that is dependent on shear stress (89). To produce adequate shear stress on the vessel wall, compression must be prompt rather than gradual.

In 2001, van Bemmelen and colleagues (90) published their long-term data using a high-pressure intermittent compression device for limb

salvage in patients who were unsuitable for surgical revascularization. The study included 14 limbs, 13 of which had forefoot tissue loss prior to treatment. These patients were considered not to be appropriate surgical candidates based on lack of target vessels, lack of conduit, previous failed bypass, or comorbid medical condition. After 3 months of treatment, the authors reported an increase in the pulse-volume recording amplitude in 70% of limbs, all of which were salvaged at maximal follow-up of 2.5 years. For the four limbs that required amputation, hidden hour counters within the compression device revealed a much lower rate of compliance in adhering to the prescribed home protocol. Patients were advised to use the device for 4 hours per day; the limb salvage group averaged 2.38 hours per day whereas the amputation group averaged 1.14 hours per day. A more recent study from Canada (91) reported 3-month limb salvage rates of 58% (or 86.4% if the renal failure patients were excluded) with the same device in a similar patient population. These studies appear to indicate that high-pressure compression therapy may be a useful addition to our treatment options for patients with limb-threatening ischemia who are unsuitable candidates for surgical revascularization.

GENE THERAPY

Gene therapy, defined as therapeutic manipulation of a gene product by either over- or underexpression, represents a novel treatment strategy for patients with critical limb-threatening lower extremity ischemia. One of the main hurdles of gene therapy has been optimizing gene delivery systems so that transfection of the desired gene product is maximal. When free DNA comes into contact with cell membranes, only a minimal amount is transported into the cell, and the little that is transported is rapidly degraded by cytoplasmic nucleases (92). Therefore, multiple vectors have been developed to facilitate DNA entry into cells. The ideal vector delivers the gene efficiently to the target tissue, allows effective gene expression for a desired time frame, has no systemic toxicity, and remains to be discovered. Most commonly used in current therapeutic trials are viral vectors, which include the retrovirus, lentivirus, adenovirus, and adeno-associated virus. Nonviral vectors include plasmids and liposomes.

Intimal Hyperplasia

The two focal areas of interest in gene therapy as it pertains to peripheral vascular disease are intimal hyperplasia and angiogenesis. Intimal hyperplasia is felt to be a result of flow perturbations, endothelial injury, and cellular proliferation. Accordingly, gene therapies for the preven-

tion of intimal hyperplasia attempt to modify the local vascular injury response and prevent cellular proliferation. A promising therapy to prevent intimal hyperplasia involves augmentation of nitric oxide production by delivery of nitric oxide synthase. Nitric oxide is a diffusible molecule that plays an important role in the vascular system via influence on endothelial maintenance, development of atherosclerosis, hypertension, vasospasm, and ischemia-reperfusion (93). It has been shown to inhibit platelet aggregation, leukocyte chemotaxis, and smooth muscle cell proliferation in addition to promoting endothelial regeneration (92). Because of these protective properties, experiments have been devised to examine the effect of increased nitric oxide production at sites of vascular injury. Several animal studies have reported a decrease in intimal hyperplasia after delivery and transduction of nitric oxide synthase to balloon-injured arterial segments compared to controls (94–96). These results are highly encouraging and suggest the great utility that nitric oxide synthase may have in preventing intimal hyperplasia. Studies are currently underway which should elucidate the effects of nitric oxide on intimal hyperplasia in the human cardiac and vascular systems.

Angiogenesis

Therapeutic angiogenesis is defined as treating ischemia by increasing the number of blood vessels within the ischemic tissue. Studies from tumor growth and cardiovascular development have identified vascular endothelial growth factors (VEGF) and fibroblast growth factors (FGF) that are expressed in response to hypoxia and cytokine release (97,98). Animal studies using VEGF and FGF have demonstrated increased collateral blood vessel development in response to the presence of limb ischemia (99,100). Baumgartner and colleagues (101) reported their data on ten limbs with critical ischemia that were treated with intramuscular injections of plasmid DNA encoding for VEGF. At an average of 6 months of follow-up, they documented an increase in ankle-brachial index from 0.33 to 0.48, newly visible collateral vessels in seven limbs, and limb salvage in eight limbs (80%). Whereas such results are encouraging, similar trials have failed to show such definite improvement. Furthermore, there are some potential drawbacks to angiogenic therapy, such as hemangioma formation, formation of nonfunctional leaky vessels, and acceleration of incidental tumor growth (92,102,103). Nonetheless, angiogenesis is a frontier that is being extensively studied and likely will have future use for limb salvage therapy in carefully selected patients.

CONCLUSION

Multiple treatment modalities exist to assist us in providing limb salvage for patients with critical lower extremity ischemia. Distal bypass with autogenous vein has clearly been shown to be the superior option, with the longest patency rates and highest rates of limb salvage. In the absence of adequate autologous vein, other conduits such as ePTFE, Dacron, and human umbilical vein may be used alone or in combination with some autologous vein (composite grafts). Percutaneous intervention, either angioplasty alone or in conjunction with stent placement, is a viable option for certain lesion types or for patients whose comorbidities preclude surgical revascularization. Therapeutic manipulation of gene expression holds great promise for future treatment in the patient with limb-threatening lower extremity ischemia.

REFERENCES

1. Hobson RW, Lynch TG, Jamil Z, et al. Results of revascularization in severe lower extremity ischemia: a five-year clinical experience. *J Vasc Surg* 1985; 2:174–182.
2. Feinglass J, Brown JL, LoSasso A, et al. Rates of lower extremity amputation and arterial reconstruction in the United States, 1979–1996. *Am J Public Health* 1999; 89:1222–1227.
3. McIntyre KE Jr. Below-Knee Amputation. In Ernst CB, Stanley JC ed: *Current Therapy in Vascular Surgery*, St. Louis, 2001, Mosby, p. 651.
4. Warren R, Kihn RB. A survey of lower extremity amputations for ischemia. *Surgery* 1968; 63:107–120.
5. McWhinnie DL, Gordon AC, Collin J, et al. Rehabilitation outcome 5 years after 100 lower limb amputations. *Br J Surg* 1994; 81:1596–1599.
6. Fletcher DD, Andrews KL, Hallett JW, et al. Trends in rehabilitation for geriatric patients with vascular disease: implications for future health resource allocation. *Arch Phys Med Rehab* 2002; 83:1389–1393.
7. Peabody CM, Kannel WB, McNamara PM. Intermittent claudication: Surgical significance. *Arch Surg* 1974; 109:693–697.
8. Imparato AM, Kim GE, Davidson TE, et al. Intermittent claudication: Its natural course. *Surgery* 1975; 78:795–799.
9. Eugene J, Goldstone J, Moore WS. Fifteen years experience with subcutaneous bypass grafts for lower extremity ischemia. *Ann Surg* 1976; 186:177–183.
10. Veith FJ, Gupta SK, Samson RH, et al. Progress in limb salvage by reconstructive arterial surgery combined with new or improved adjunctive procedures. *Ann Surg* 1981; 194:386–401.
11. Taylor LM Jr., Edwards JM, Porter JM. Present status of reversed vein bypass grafting: five-year results of a modern series. *J Vasc Surg* 1990; 11:193–206.
12. Belkin M, Knox J, Donaldson MC, et al. Infrainguinal arterial reconstruction with nonreversed greater saphenous vein. *J Vasc Surg* 1996; 24:957–962.
13. May AG, DeWeese JA, Rob CG. Arterialized “in-situ” saphenous vein. *Arch Surg* 1965;91:743–750.

14. Carney WI Jr., Balko A, Barrett MS. *In situ* femoropopliteal and infrapopliteal bypass. *Arch Surg* 1985; 120:812–816.
15. Bush HL Jr., Nadseth DC, Curl GR. In situ saphenous vein bypass grafts for limb salvage. *Am J Surg* 1985; 148:477–480.
16. Hurley JJ, Auer AI, Binnington HB, et al. Comparison of initial limb salvage in 98 consecutive patients with either reversed autogenous or in situ vein bypass graft procedures. *Am J Surg* 1985; 150:777–781.
17. Holzenbein TJ, Pomposelli FB Jr., Miller A, et al. Results of a policy with arm veins used as the first alternative to an unavailable ipsilateral greater saphenous vein for infrainguinal bypass. *J Vasc Surg* 1996; 23:130–140.
18. Campbell CD, Brooks DH, Webster MW, et al. The use of expanded microporous polytetrafluoroethylene for limb salvage: a preliminary report. *Surgery* 1976; 9:485–491.
19. Abbott WM, Green RM, Matsumoto T, et al. Prosthetic above-knee femoropopliteal bypass grafting: results of a multicenter randomized prospective trial. *J Vasc Surg* 1997; 25:19–28.
20. Veith FJ, Gupta SK, Ascer E, et al. Six-year prospective multicenter randomized comparison of autologous saphenous vein and expanded polytetrafluoroethylene grafts in infrainguinal arterial reconstructions *J Vasc Surg* 1986; 3:104–114.
21. Sterpetti AV, Schultz RD, Feldhaus RJ, et al. Seven-year experience with polytetrafluoroethylene as above-knee femoropopliteal bypass graft. Is it worthwhile to preserve the autologous saphenous vein? *J Vasc Surg* 1985; 2:907–912.
22. Klinkert P, Schepers A, Burger DHC, et al. Vein versus polytetrafluoroethylene in above-knee femoropopliteal bypass grafting: Five-year results of a randomized clinical trial. *J Vasc Surg* 2003; 37:149–155.
23. Bergan JJ, Veith FJ, Bernhard VM, et al. Randomization of autogenous vein and polytetrafluoroethylene grafts in femoral–distal reconstruction. *Surgery* 1982; 92:921–930.
24. Raptis S, Miller JH. Influence of vein cuff on polytetrafluoroethylene grafts for primary femoropopliteal bypass. *Br J Surg* 1995; 82:487–491.
25. Stonebridge PA, Prescott RJ, Ruckley CV. Randomized trial comparing infrainguinal polytetrafluoroethylene bypass grafting with and without vein interposition cuff at the distal anastomosis. The Joint Vascular Research Group. *J Vasc Surg* 1997; 26:543–550.
26. Abbott WM, Megerman J, Hasson JE, et al. Effect of compliance mismatch on vascular graft patency. *J Vasc Surg* 1987; 5:376–382.
27. Zwolak RM, Adams MC, Clowes AW. Kinetics of vein graft hyperplasia: Association with tangential stress. *J Vasc Surg* 1987; 5:126–136.
28. Bastounis E, Georgopolis S, Maltezos C, et al. PTFE-vein composite grafts for critical limb ischemia: A valuable alternative to all-autogenous infrageniculate reconstructions. *Eur J Vasc Endovasc Surg* 1999; 18:127–132.
29. McCarthy WJ, Pearce WH, Flinn WR, et al. Long-term evaluation of composite-sequential bypass for limb threatening ischemia. *J Vasc Surg* 1992; 15:761–770.
30. Roddy SP, Darling RC, Ozsvath KJ, et al. Composite sequential arterial reconstruction for limb salvage. *J Vasc Surg* 2002; 36:325–329.
31. Dardik H, Ibrahim IM, Dardik I. Modified and unmodified umbilical vein allograft and xenografts employed as arterial substitutes: A morphologic assessment. *Surg Forum* 1975; 26:286.
32. Dardik I, Dardik H. The fate of human umbilical cord vessels used as interposition arterial grafts in the baboon. *Surg Gynecol Obstet.* 1975; 140:567.

33. Johnson WC, Lee, KK. A comparative evaluation of polytetrafluoroethylene, umbilical vein, and saphenous vein bypass grafts for femoral-popliteal above-knee revascularization: A prospective randomized Department of Veterans Affairs cooperative study. *J Vasc Surg* 2000; 32:268–277.
34. Dardik H, Miller N, Dardik A, et al. A decade of experience with the gluteraldehyde tanned human umbilical cord vein graft for revascularization of the lower limb. *J Vasc Surg* 1988; 7:336–346.
35. Hasson JE, Newton WD, Waltman AC, et al. Mural degeneration in the gluteraldehyde-tanned umbilical vein graft: incidence and implications. *J Vasc Surg* 1986; 4:243–250.
36. Aalders GJ, Van Vroonhoven T. Polytetrafluoroethylene versus HUV in AK femoropopliteal bypass: Six-year results of randomized clinical trail. *J Vasc Surg* 1992; 6:816–824.
37. Jarrett F, Mahood BA. Long-term results of femoropopliteal bypass with stabilized HUV. *Am J Surg* 1994; 168:111–114.
38. LoGerfo FW, Quist WC, Cantelmo NL, et al. Integrity of vein grafts as a function of initial intimal and medial preservation. *Circulation* 1983; 68:II117–II124.
39. Zilla P, Von Oppell U, Deutsch M. The endothelium: a key to the future. *J Card Surg* 1993; 8:32–60.
40. Deutsch M, Meinhart J, Fischlein T, et al. Clinical autologous vein in vitro endothelialization of infrainguinal ePTFE grafts in 100 patients: a 9-year experience. *Surgery* 1999; 126:847–855.
41. Prager M, Holzenbein T, Aslim E, et al. Fresh arterial homograft transplantation: A novel concept for critical limb ischemia. *Eur J Vasc Endovasc Surg* 2002; 24:314–321.
42. Ellis P, Muller-Schweinitzer E. Maintenance of functional activity of human pulmonary arteries after cryopreservation. *Br J Pharmacol* 1991; 103:1377–1380.
43. Schoeffter P, Muller-Schweinitzer E. The preservation of functional activity of smooth muscle and endothelium in pig coronary arteries after storage at –190 degrees C. *J Pharm Pharmacol* 1990; 42:646–651.
44. Albertini JN, Barral X, Branchereau A, et al. Long-term results of arterial allograft below-knee bypass grafts for limb salvage: A retrospective multicenter study. *J Vasc Surg* 2000; 31:426–435.
45. Serletti JM, Deuber MA, Guidera PM, et al. Atherosclerosis of the lower extremity and free-tissue reconstruction for limb salvage. *Plast Reconstr Surg* 1995; 96: 1136–1144.
46. McCarthy WJ, Matsamura JS, Fine, NA et al. Combined arterial reconstruction and free tissue transfer for limb salvage. *J Vasc Surg* 1999; 29:814–820.
47. Ewing M. The history of lumbar sympathectomy. *Surgery* 1971;70:791–795.
48. Cronenwett JL, Lindenaer SM. Hemodynamic effects of sympathectomy in ischemic canine limbs. *Surgery* 1980; 87:417–424.
49. Cronenwett JL, Zelenock JB, Whitehouse W Jr., et al. The effect of sympathetic innervation on canine muscle and skin blood flow. *Arch Surg* 1983; 118:420–424.
50. Simeone FA. Intravascular pressure, vascular tone and sympathectomy. *Surgery* 1963;53:1–18.
51. Persson AV, Anderson L, Rodberg FT Jr. Selection of patients for lumbar sympathectomy. *Surg Clin North Am* 1985; 65:393–403.
52. Yao JST, Bergan JJ. Predictability of vascular reactivity relative to sympathetic ablation. *Arch Surg* 1973; 107:676–681.

53. Rutherford RB. Role of sympathectomy in the management of vascular disease and related disorders. In Moore WS, *Vascular Surgery: A Comprehensive Review*. Philadelphia, 2002, WB Saunders, p. 372.
54. Collins GJ Jr., Rich NM, Clagett GP, et al. Clinical results of lumbar sympathectomy. *Am Surg* 1981;47:31–35.
55. Haimovici H, Steinman C, Karson IH. Evaluation of lumbar sympathectomy: Advanced occlusive arterial disease. *Arch Surg* 1964; 89:1089–1095.
56. Szilagyi DE, Smith RF, Scarpella JR, et al. Lumbar sympathectomy: Current role in the treatment of arteriosclerotic occlusive disease. *Arch Surg* 1967; 95:753–761.
57. Walker PM, Johnston KW. Predicting the success of a sympathectomy: A prospective study using discriminant function and multiple regression analysis. *Surgery* 1980; 87:216–221.
58. Johnston KW, Rae M, Hogg-Johnston SA, et al. 5-year results of a prospective study of percutaneous transluminal angioplasty. *Ann Surg* 1987; 206:403–413.
59. O'Mara CS, Neiman HL, Flinn WR, et al. Hemodynamic assessment of transluminal angioplasty for lower extremity ischemia. *Surgery* 1981; 89:106–117.
60. Cole SE, Baird RN, Horrocks M, et al. The role of balloon angioplasty in the management of lower limb ischemia. *Eur J Vasc Surg* 1987; 1:61–65.
61. Schoop W, Levy H, Cappius G, et al. Early and late results of PTD in iliac stenosis. In Zeitler E, Gruntzig A, Schoop W, eds, *Percutaneous Vascular Recanalization*. Berlin, 1978, Springer-Verlag, pp. 111–117.
62. Palmaz JC, Laborde JC, Rivera FJ, et al. Stenting of the iliac arteries with the Palmaz stent: experience with a multicenter trial. *Cardiovasc Intervent Radiol* 1992; 15:291–297.
63. Martin EC, Katzen BT, Benenati JF, et al. Multicenter trial of the Wallstent in the iliac and femoral arteries. *J Vasc Interv Radiol* 1995; 6:843–849.
64. Strecker EP, Boos IBL, Hagen B. Flexible tantalum stents for the treatment of iliac artery lesions: long-term patency, complications, and risk factors. *Radiology* 1996; 204:87–96.
65. Bosch JL, Hunink MGM, Meta-analysis of the results of percutaneous transluminal angioplasty and stent placement for aortoiliac occlusive disease. *Radiology* 1997; 204:87–96.
66. Richter GM, Noeledge G, Roeren T, et al. First long-term results of a randomized multicenter trial: iliac balloon-expandable stent placement versus regular percutaneous transluminal angioplasty. *Radiology* 1990; (abstract)177:152.
67. Richter GM, Roeren T, Brado M, et al. Further update of the randomized trail: iliac stent versus PTA-morphology, clinical success rates, and failure analysis. *J Vasc Interv Radiol* 1993; (abstract)4:30–31.
68. Johnston KW. Femoral and popliteal arteries: Reanalysis of results of balloon angioplasty. *Radiology* 1992; 183:767–771.
69. Treiman GS, Treiman RL, Ichikawa L, et al. Should percutaneous transluminal angioplasty be recommended for treatment of infrageniculate popliteal artery or tibio-peroneal trunk stenosis? *J Vasc Surg* 1995; 22:457–463.
70. White GH, Liew SCC, Waugh RC, et al. Early outcome and intermediate follow-up of vascular stents in the femoral and popliteal arteries without long-term anticoagulation. *J Vasc Surg* 1995; 21:270–281.
71. Bergeron P, Pinot JJ, Poyen V, et al. Long-term results with the Palmaz stent in the superficial femoral artery. *J Endovasc Surg* 1995;2:161–167.
72. Saproval MR, Long AL, Raynaud AC, et al. Femoropopliteal stent placement: long-term results. *Radiology* 1992; 184:833–839.

73. Rousseau HP, Raillat CR, Joffre FG, et al. Treatment of femoropopliteal stenosis by means of self-expandable endoprosthesis: midterm results. *Radiology* 1989; 172:961–964.
74. Do-Dai-Do, Triller J, Walpoth BH, et al. A comparison study of self-expandable stents vs balloon angioplasty alone in femoropopliteal artery occlusions. *Cardiovasc Intervent Radiol* 1992; 15:306–312.
75. Gray BH, Sullivan TM, Childs MB, et al. High incidence of restenosis/reocclusion of stents in the percutaneous treatment of long-segment superficial femoral artery disease after suboptimal angioplasty. *J Vasc Surg* 1997; 25:74–83.
76. Bolia A, Miles KA, Brennan J, et al. Percutaneous transluminal angioplasty of occlusions of the femoral and popliteal arteries by subintimal dissection. *Cardiovasc Intervent Radiol* 1990; 13:357–363.
77. Reekers JA, Kromhout JG, Jacobs MJ. Percutaneous intentional extraluminal recanalisation of the femoropopliteal artery. *Eur J Vasc Surg* 1994; 8:723–728.
78. London NJ, Srinivasan R, Naylor AR, et al. Subintimal angioplasty of femoropopliteal artery occlusions: the long-term results. *Eur J Vasc Surg* 1994;8:148–155.
79. McCarthy RJ, Neary W, Roobottom C, et al. Short-term results of femoropopliteal subintimal angioplasty. *Br J Surgery* 2000; 87:1361–1365.
80. Ingle H, Nasim A, Bolia A, et al. Subintimal angioplasty of isolated infragenicular vessels in lower limb ischemia: long-term results. *J Endovasc Therapy* 2002; 9:411–416.
81. Vraux H, Hammer F, Verhelst R, et al. Subintimal angioplasty of tibial vessel occlusions in the treatment of critical limb ischemia: mid-term results. *Eur J Vasc Endovasc Surg* 2000; 20:441–446.
82. Nydahl S, Hartshorne T, Bell PR, et al. Subintimal angioplasty of infrapopliteal occlusions in critically ischaemic limbs. *Eur J Vasc Endovasc Surg* 1997; 14: 212–216.
83. Murray J. On the local and general influence on the body of increased and diminished atmospheric pressure. *Lancet* 1835; 1:909–917.
84. Delis K, Azizi ZA, Nicolaidis AN, et al. Determining the optimum intermittent pneumatic compression (IPLC) stimulus for lower limb venous emptying using direct pressure measurements. *Br J Surg* 1996; (abstract):83(suppl 2):148.
85. Van Bemmelen PS, Ricotta JJ. Mechanical pump in the treatment of chronic limb-threatening ischemia. In Pearce WH, Matsamura JS, Yao JST, eds. *Trends in Vascular Surgery*, Chicago, 2002, Precept Press, pp. 45–66.
86. Lamontagne D, Pohl U, Busse R. Mechanical deformation of the vessel wall and shear stress determine the basal release of endothelium-derived relaxing factor in the intact rabbit coronary vascular bed. *Circ Res* 1992; 70:123–130.
87. Dai G, Tsukurov O, Orkin RW, et al. An in vitro cell culture system to study the influence of external pneumatic compression on endothelial function. *J Vasc Surg* 2000; 32:977–987.
88. Liu K, Chen L, Seaber AV, et al. Influences of inflation rate and duration on vasodilatory effect by intermittent pneumatic compression in distant skeletal muscle. *J Orthop Res* 1999; 17:415–420.
89. Liu K, Chen L, Seaber AV, et al. Intermittent pneumatic compression of legs increases microcirculation in distant skeletal muscle. *J Orthop Res* 1999; 17:88–95.
90. Van Bemmelen PS, Gitlitz DB, Faruqi RM, et al. Limb salvage using high-pressure intermittent compression arterial assist device in cases unsuitable for surgical revascularization. *Arch Surg* 2001; 136:1280–1285.

91. Louridas G, Saadia R, Spelay J, et al. The ArtAssist device in chronic lower limb ischemia. A pilot study. *Int Angiol* 2002; 21:28–35.
92. Zuckerbraun BS, Tzeng E. Vascular gene therapy. A reality of the 21st century. *Arch Surg* 2002; 137:854–861.
93. Moncada S. Nitric oxide in the vasculature: physiology and pathophysiology. *Ann NY Acad Sci* 1997; 811:60–67.
94. Von der Leyen HE, Gibbons GH, Morishita R, et al. Gene therapy inhibiting neointimal vascular lesion: in vivo transfer of endothelial cell nitric oxide synthase gene. *Proc Natl Acad Sci USA* 1995; 92:1137–1141.
95. Tzeng E, Shears L II, Robbins PD, et al. Vascular gene transfer of the human inducible nitric oxide synthase: characterization of activity and effects on myointimal hyperplasia. *Mol Med* 1996; 2:221–225.
96. Shears L II, Kibbe MR, Murdock AD, et al. Efficient inhibition of intimal hyperplasia by adenovirus-mediated inducible nitric oxide synthase gene transfer to rats and pigs in vivo. *J Am Coll Surg* 1998; 187:295–306.
97. Neufeld G, Cohen T, Gengrinovitch S, et al. Vascular endothelial growth factor (VEGF) and its receptors. *FASEB J* 1999; 13:9–22.
98. Petrova TV, Makinen T, Alitalo K. Signaling via vascular endothelial growth factor receptors. *Exp Cell Res* 1999; 253:117–130.
99. Takeshita S, Zheng LP, Brogi E, et al. Therapeutic angiogenesis: a single intra-arterial bolus of vascular endothelial growth factor augments revascularization in a rabbit ischemic hind limb model. *J Clin Invest* 1994; 93:662–670.
100. Balfour R, Berman J, Garb JL, et al. Enhanced angiogenesis and growth of collateral by in vivo administration of recombinant basic fibroblast growth factor in a rabbit model of acute lower limb ischemia: dose-response effect of basic fibroblast growth factor. *J Vasc Surg* 1992; 16:181–191.
101. Baumgartner I, Pieczek A, Manor O, et al. Constitutive expression of phVEGF165 after intramuscular gene transfer promotes collateral vessel development in patients with critical limb ischemia. *Circulation* 1998; 97:1114–1123.
102. Lee RJ, Springer ML, Blanco-Bose WL, et al. VEGF gene delivery to myocardium: deleterious effects of unregulated expression. *Circulation* 2000; 102:898–901.
103. Carmeliet P. VEGF gene therapy: stimulating angiogenesis or angioma-genesis? *Nat Med* 2000; 6:1102–1103.

Index

A

- ABCA1 and cholesterol efflux, 144
- Abdominal aortic aneurysm (AAA)
and intermittent claudication,
3, viii
- ABI. *See* Ankle-brachial index (ABI)
- Adenosine for LEAD, 190–192,
207–208, ix
- Adiponectin and inflammation, 107
- ADMA (Asymmetric
dimethylarginine), 105–106, 112
- ADMIT trial, 203
- ADVENT trial, 202
- Advicor (lovastatin + niacin), 205, 235
- AFCAPS/TexCAPS (Air Force/
Texas Coronary Atherosclerosis
Prevention Study), 63–64
- Albumin, sonicated (Optison), 192
- Alcohol and PAD, 110–111
- Allografts, 275–276
- Amputation
for claudication, 7, 238
and diabetes, 7, 55, 56, 80
for LEAD, 8
for PAD, 80
- Aneurysms, formation of, 276
- Angina, 106, 224
- Angiogenesis, promoting, 229, 286
- Angiogenic growth factors for
LEAD/CAD, 229
- Angiography. *See also* Magnetic
resonance angiography (MRA)
diagnosis using, 34, 36, 258, 259
LOCAT trial, 200–201
- Angioplasty
complications of, 264
iliac with stenting, 280–281
infrainguinal with stenting, 281–283
percutaneous, 257, 279–281
POBA, 259, 265, 266, 279
PTA, 262–264
subintimal, 283–284
- Angiotensin converting enzyme
inhibitors (ACEIs), 193, 232
- Angiotensin II, effects of, 122–124
- Angiotensin receptor blockers
(ARBs), 193, 233
- Ankle-brachial index (ABI)
and cilostazol, 227
diagnosis using, 9, 25–27, 187
and heart disease prognosis, 188, viii
PAD prognosis and, 57
and prognosis, 206–207
- Annexin II, function of, 103
- Antioxidant defenses, 138–139
- Antiplatelet therapy, 236–238, 246
- Apoprotein A (Apo A), function of,
141–144
- Apoprotein B (Apo B)
and CAD/LEAD, 185
function of, 137–138
- ARBITER study, 194–195, 234
- L-arginine and lesion formation, 106
- ARIC (Atherosclerosis Risk in Com-
munities) study, 112, 128, 131,
133, 140–141
- Arterial stenosis, diagnosis via
duplex scanning, 28–35
- Arteriography in diagnosis, 29, 34
- Aspirin and niacin, 204
for skin flushing, 202–205, 235
as therapy, 237

- Asymmetric dimethylarginine (ADMA), 105–106, 112
- AT1 receptor and AII, 124
- Atherectomy, 264
- Atheroma, pathology of, 119–122, 134
- Atherosclerosis
- antagonists, physiological, 151
 - cathepsins in, 150
 - cholestyramine for, 65, 68
 - colestipol for, 67, 68
 - C reactive protein (CRP) in, 117
 - described, 75, 243
 - DHEA-S in, 131
 - diet and, 68, 108–109, 114
 - in endothelial cells (ECs), 101–102, 106
 - and the endothelium, 105
 - E-/P-selectins in, 114
 - fibrates and, 65–66, 200–201
 - and fibrinogen levels, 103
 - high-density lipoproteins (HDLs) in, 142–146, 151
 - and hypertension, 79–80, 100
 - immune reactions in, 115–116
 - immunoglobulins in, 125
 - infections in, 118–119
 - inflammation in, 113–118
 - intervention trials in, 63–64
 - lipids, lowering, 63–65, 69
 - 15-lipoxygenase in, 133–134
 - and lipoprotein A (LpA), 140–142, 151
 - lovastatin for, 64, 65, 205
 - low-density lipoproteins (LDLs), 131
 - and microalbuminuria, 101
 - mitogens and, 122–123
 - monounsaturated fatty acids (MUFAs) in, 108–109
 - NFκB pathway in, 117, 135
 - niacin and, 66–68
 - obesity in, 109–110
 - pathogenesis of, 23–24, 62, 69, 75–76, 102, 125, 145
 - pravastatin for, 65
 - premature, 145
 - preventing, 109, 138–139
 - probucol for, 68
 - progesterone in, 130
 - proteoglycans and, 150
 - regression in, 195
 - risk factor modification, 231–233
 - risk factors for, 62–63, 76–81, 100–101, 110
 - sex hormones in, 129–131
 - simvastatin for, 64, 68–69
 - and smoking, 76, 78, 111–112, 231
 - statins and, 64–65
 - stress in, 101–102, 128–129
 - studies of (*See individual study by name or acronym*)
- Atherosclerosis Risk in Communities (ARIC) study, 112, 128, 131, 133, 140–141
- Atorvastatin, 65, 196
- Atorvastatin Versus Revascularization Treatments (AVERT), 65
- Autogenous vein conduits, 272–274
- AVERT (Atorvastatin vs Revascularization Treatments), 65
- B**
- β-blockers
- for claudication, 2, 193
 - for hypertension, 233
 - for MI, 206
 - and Raynaud's phenomenon, 15
 - and smoking, 43
- BECAIT trail, 66
- Bezafibrate and CAD, 66, 200
- Bile salt dependent lipase, 139
- Bleomycin and Raynaud's phenomenon, 15
- Bone marrow cells, 122
- Buerger's disease described, 10

Bupropion SR, 47, 48, 206, 231

C

CABG. *See* Coronary artery bypass graft (CABG)

CAD. *See* Carotid artery disease (CAD); Coronary Artery Disease (CAD)

Calcium channel blockers (CCBs)
for hypertension, 233
for MI, 206

and Raynaud's phenomenon, 16

Calcium deposits and CAD, 188

Canadian Coronary Atherosclerosis Intervention Trial (CCAIT), 64

CAPRIE trial, 237

Cardiac myxoma described, 3

Cardiovascular disease (CVD)

exercise and, 86–90, 92–95

mortality studies, 87–93

obesity and, 86, 100

plaques in, 54–55

prognosis, 126

risk factors for, 40–43, 86,
90–91, 101

and stress, 129

CARE (Cholesterol and Recurrent Events) study, 65

Carotid artery disease (CAD)

and alcohol, 110

and CAD/LEAD, 7, 206

causes of, 86, 197–199

management, 194

Casteldaccia study of PAD, 57–58, 81

Cathepsins in atherosclerosis, 150

CCAIT (Canadian Coronary Atherosclerosis Intervention Trial), 64

CCBs. *See* Calcium channel blockers (CCBs)

CD40 in immune response, 116

CETP (Cholesteryl ester transfer protein) and HDLs, 142, 143

CHD. *See* Coronary heart disease (CHD)

Chemokine receptor 2 (CCR2) in monocyte recruitment, 114

Chemokines in inflammation, 113

CHF. *See* Congestive heart failure (CHF)

Chlorthalidone, 233

Cholesterol and Recurrent Events (CARE) study, 65

Cholesterol Lowering Atherosclerosis Study (CLAS), 66–68

Cholesteryl ester transfer protein (CETP) and HDLs, 142, 143

Cholestyramine for atherosclerosis, 65, 68

Chymase, function of, 104

Cilostazol, 224, 226–231

CLAS (Cholesterol Lowering Atherosclerosis Study), 66–68

Claudication. *See* Intermittent claudication; Pseudoclaudication

Clonidine, 47

Clopidogrel, 193, 237

Clusterin/Apo J and senescence, 139

Cocaine and Raynaud's phenomenon, 15

Colestipol for atherosclerosis, 67, 68

Color flow duplex scanning
described, 27–35

Computed tomography (CT), 188, 209

Conduits for surgery, 272–276

Congestive heart failure (CHF), 77, 228

Continuous wave (CW) Doppler ultrasound
described, 25–27

Cooper Clinic study of exercise, 92–93

Copenhagen Male Study, 198

Copper-zinc superoxide dismutase (CuZn-SOD) and LDL oxidation, 134–135

Corn oil and endothelial damage, 109

Coronary artery bypass graft (CABG)

- and LEAD, 207, 211
- and lipid lowering, 65
- LOCAT results, 200
- niacin therapy for, 203
- Coronary Artery Disease (CAD)
 - and claudication, 7, 9
 - and diabetes, 53, 54, 150
 - diagnosis, 103, 186, 188, ix
 - in elderly patients, 8, 129
 - growth factors and, 229
 - hepatic lipase (HL) and, 140
 - hyperinsulinemia in, 107
 - and LEAD, 183–188, 193, 206, 207, 235
 - oxidative stress in, 138
 - oxLDL in, 115–116
 - platelet activation in, 104
 - polyunsaturated fatty acids (PUFA), 108
 - prevention of, 66, 77, 88–89
 - prognosis, 188
 - risk factors for, 86, 90–92, 100, 131, 136, 150, 205
 - sphingomyelin and, 131
 - treatment of, 66, 200–201, vii
- Coronary Drug Project, 66, 203
- Coronary heart disease (CHD)
 - management, 194, 203
 - mortality in, 119–120
 - PON activity in, 145
 - prevalence of, 129
 - risk factors for, 100–101, 112, 143
- C reactive protein (CRP), 110, 117
- CREST and Raynaud's phenomenon, 14
- Crestor (Rosuvastatin), 201, 204, 235
- CRP. *See* C reactive protein (CRP)
- Cryopreservation of allografts, 276
- CVD. *See* Cardiovascular disease (CVD)
- Cyanosis in LEAD, 10
- Cyclosporine and statins, 196–197
- Cytokines
 - and immune response, 116, 118, 128
 - in LEAD, 199
 - and proteoglycans, 148–149
- D**
- DHEA-S in atherosclerosis, 131
- Diabetes Control and Complication Trials, 232
- Diabetes mellitus
 - amputation rate for, 7, 55, 56, 80
 - and arteriosclerosis, 5, 126
 - in CAD, 53, 54, 150
 - Diabetes Control and Complication Trials, 232
 - exercise and, 245
 - and hypertension, 78, 80, 81, 233
 - LDL oxidation and, 136–138
 - LEAD and, 185, 199, 231–232, 236
 - and niacin, 202, 203
 - occlusion and, 24
 - and PAD, 53–58
 - prevalence of, 53
 - United Kingdom Prospective Diabetes Study, 232
- Diet
 - ACE activity and, 124
 - and atherosclerosis, 68, 108–109, 114
 - HDLs and, 146
 - and therapy, 235–236
- Dipyridamole (persantine IV)
 - and adenosine, 190–192
 - administration method, 190
 - for LEAD, 207–208
- Dislipidemia, 185, 205, 245. *See also* Lipids
- Diuretics for hypertension, 233
- Dobutamine
 - for LEAD, 191–192, 208, ix
 - stress echocardiography, 192–194
- Doppler ultrasound, 9, 11

Dual isotope IV injection, 189

E

Edinburgh Claudication

Questionnaire described, 4, 6

EGF (Epidermal growth factor), 127

Elderly patients

claudication in, 7–10

and exercise, 247

hypertension in, 79

osteoprotegerin (OSP) in CAD, 150

pseudoclaudication in, 12–13

Electromagnetic flowmetry, 9

Endarterectomy, 271

Endothelial cells (ECs). *See also*

Endothelium

apoptosis, inducing, 106–107

atherosclerosis in, 101–102, 106

and modified LDLs, 135–136

and proteoglycans, 106

Endothelial lipase and HDLs, 146

Endothelin-converting enzyme

(ECE)-1, 117

Endothelium. *See also* Endothelial cells (ECs)

dysfunction in, 105, 109, 124

function, preserving, 273

interactions in, 114

Epidermal growth factor (EGF), 127

Ergotamine derivatives, complications of, 10, 15

Erythromycin and statins, 196–197

Estrogens, 124, 129

Estrones in atherosclerosis, 130

Exercise

and CAD/LEAD, 184, 235

and cardiovascular disease

(CVD), 86–90, 93–95

CHF and, 93–95

and CVD, 86–90, 92–95

duration/frequency/length, 249, 252–253

ECG changes and, 89

intensity, 248

limitations of, 249–250, 253

mode of, 247–248, 251–252

prevention, mechanisms of, 94–95, 250–251

vs surgery, 246

therapy

for LEAD, 243–253

rationale for, 244–250

thresholds, beneficial, 88

Extracellular matrix (EM)

degradation of, 149–150

and lipoproteins, interactions, 148–149

production of, 147–148

in vascular calcification/ossification, 150–151

Ezetimibe (Zetia), 201, 204, 235

F

Familial Atherosclerosis Treatment Study (FATS), 66–67

Family Heart Study, 111

FATS (Familial Atherosclerosis Treatment Study), 66–67

Felodipine and statins, 196–197

Fenofibrate, 195, 201, 204, 205, 234, 235

FGFs (Fibroblast growth factors), role of, 127, 229, 286

Fibrates. *See also individual drug by name*

and atherosclerosis, 65–66, 200–201

and HDL-C levels, 199

statins and, 195, 234

Fibric acid derivatives for LEAD, 199–200

Fibrinogen levels

and atherosclerosis, 103

and CAD/LEAD, 186

- and smoking, 42
- Fibroblast growth factors (FGFs),
 - role of, 127, 229, 286
- Fish oil and blood lipids, 109
- Foot, claudication of, 2
- Fractalkine (CX3CLI) in inflammation, 113–114
- Framingham Heart Study
 - arterial disease, prevalence of, 5–6
 - and atherosclerosis, 76, 100
 - HDL-C in, 197
 - hypertension in, 76–78
 - and PAD/diabetes, 54
 - smoking and stroke incidence, 41, 42
- G**
- γ A/ γ fibrinogen described, 103
- Gemfibrozil
 - and CAD, 66, 200–201
 - and statins, 201
- Gene therapy, 229, 230, 285–286
- Glucose intolerance
 - and niacin, 202
 - and PAD, 57, 81
- Glycolytic pathways and LEAD
 - performance, 248
- Grafts, 271–272, 274–275
- Growth factors and proteoglycans, 148–149. *See also individual growth factor by name*
- H**
- HDLs. *See* High-density lipoproteins (HDLs)
- Heart and Estrogen/Progestin Replacement Study (HERS), 130
- Heart Outcomes Prevention Evaluation (HOPE) trial, 232, 233
- Heart Protection Study, 195, 196
- Helsinki Heart Study, 63–64, 66
- Hemodynamic testing described, 24, 29
- Heparan sulfate in ECs, 106–107
- Hepatic lipase (HL) and CAD, 140
- HERS (Heart and Estrogen/Progestin Replacement Study), 130
- High-density lipoproteins (HDLs)
 - in atherosclerosis, 142–146, 151
 - and CETP, 142, 143
 - HDL-C, 197–201, 203–204, 234
 - metabolism of, 146–147
 - oxidation of, 144–145
 - VAHIT trial, 66, 200
- High-pressure intermittent compression, 284–285
- Homocysteine (Hcy)
 - and CAD/LEAD, 186, 205
 - and estrogen, 130
 - in lipid oxidation, 112–113
- Honolulu Heart Program, 142
- HOPE (Heart Outcomes Prevention Evaluation) trial, 232, 233
- Hormone replacement therapy (HRT), 129–131
- HRT. *See* Hormone replacement therapy (HRT)
- HSP and atherosclerosis, 118
- Hydrochlorothiazide, 233
- Hypercholesteremia
 - and AT1, 124
 - and CHD, 100
 - health issues of, 112, 124
 - and PAD, 58, 63, 78, 81
 - PQRST study and, 68
- Hyperglycemia and LDL oxidation, 136–137
- Hyperhomocysteinemia, 112
- Hyperinsulinemia, 107, 199
- Hyperlipidemia. *See also* Lipids
 - in ARIC study, 131
 - in PAD, 61–70, 80
 - POSCH study, 66, 68
- Hypertension
 - atherosclerosis and, 79–80, 100

- and diabetes, 78, 80, 81, 233
 - exercise and, 245
 - and organ damage, 78
 - PAD and, 58, 75–81
 - as risk factor, 187, 232, 233
 - shear stress in, 101
 - SHEP (Systolic Hypertension in the Elderly Program), 79, 187
 - treatment of, 233
- Hypertriglyceridemia
- in CAD/LEAD, 109, 185, 198, 201
 - and obesity, 110
 - treatment of, 195, 234
- Hyperuricemia, 107
- ## I
- ICAM-1 in endothelial interactions, 114
- Immune reactions
- in atherosclerosis, 115–116
 - cytokines and, 116, 118, 128
 - interferons in, 116
 - interleukins in, 116, 119, 128
- Immunoglobulins, 125, 137
- Infections in atherosclerosis, 118–119
- Inflammation
- Adiponectin and, 107
 - in atheroma, 119
 - in atherosclerosis, 113–118
 - and CAD/LEAD, 186, 199
 - chemokines in, 113
 - Fractalkine (CX3CL1) in, 113–114
 - and lipoproteins, 117, 126
 - and LpA, 141
 - tumor necrosis factor α (TNF- α), 114–115, 128
- Insulin
- in atherosclerosis, 125, 126
 - and CAD, 100
 - and LDL oxidation, 137
 - and obesity, 109–110
 - resistance to, 107, 110, 128–129, 185
- Interferon γ in immune response, 116
- Interleukins
- in immune response, 116, 119, 128
 - in LEAD, 199
- Intermittent claudication
- causes of, 3, 10–11, 54, viii
 - described, 1–2, 61–62, 238
 - diagnosis, 4, 6–11, 29, 34, 187, 210
 - management of, 2, 7, 43, 67, 193, 224, 238, 262–264
 - prevalence of, 5, 224
 - prognosis, 7
 - risk factors for, 62–63, 78
 - symptoms, mechanism of, 223–224
- Intimal hyperplasia, 285–286
- Iron and atherosclerotic progression, 140
- ## J
- Job activity and CVD protection, 88–90
- Joint National Committee on Hypertension, 233
- ## K
- Ketanserin and Raynaud's phenomenon, 16
- Ketoconazole and statins, 196–197
- ## L
- LDLs. *See* Low-density lipoproteins (LDLs)
- LEAD. *See* Lower Extremity Arterial Disease (LEAD)
- Lecithin:cholesterol acyltransferase (LCAT) and HDLs, 142, 143
- Limb scintigraphy in diagnosis, 9
- Linoleic acid, function of, 109
- LIPID (Long Term Intervention with Pravastatin in Ischemic Disease) study, 65
- Lipid Research Clinic study, 91–92, 197

- Lipids. *See also* Dislipidemia;
Hyperlipidemia
accumulation of, 139, 148
fish oil and, 109
Lipid Research Clinic study,
91–92, 197
Lipid-Treatment Assessment
Project (L-TAP), 69
lowering
and atherosclerosis, 63–65, 69
in PAD, 67–69
oxidation of, 112–113, 145
and proteoglycans, 148
Lipid-Treatment Assessment Project
(L-TAP), 69
15-lipoxygenase in atherosclerosis,
133–134
Lipoprotein A (LpA)
and atherosclerosis, 140–142, 151
and CAD/LEAD, 185–186, 205
niacin and, 202
Lipoprotein lipase (LPL), 132–133
Lipoproteins. *See also* High-density
lipoproteins (HDLs); Low-
density lipoproteins (LDLs)
and the ECM, 149
and inflammation, 117, 126
niacin and, 201–202
LOCAT (Lipid Coronary Angiography
Trial), 200–201
Long Term Intervention with
Pravastatin in Ischemic
Disease (LIPID) study, 65
Lipid Coronary Angiography Trial
(LOCAT), 200–201
Los Angeles Atherosclerosis Study, 130
Losartan, 233
Lovastatin
Advicor (lovastatin + niacin),
205, 235
for atherosclerosis, 64, 65, 205
Low-density lipoproteins (LDLs)
atherosclerosis and, 131
catabolism of, 104
enzymatically modified, 135
extra-low (LDL-C), 194–197,
234–236
modification of, 135–138
oxidation, 111, 134–138, 145
oxLDL
atherogenicity of, 134
in CAD, 115–116
and dendritic cells, 117–118
in ECs, 106
function of, 114
and monocytes, 136
and proteoglycans, 148–149
reduction of, 65
and smoking, 42
uptake of, 131–133
Lower Extremity Arterial Disease
(LEAD)
adenosine, 190–192, 207–208, ix
amputation for, 8
Atorvastatin for, 196
and CAD, 206, 207, 245, viii
classification of, 244
coronary artery bypass graft
(CABG), 207, 211
coronary artery disease (CAD),
183–188, 193, 206, 207, 235
diagnosis, 24–37, 185 (*See also*
individual test by name)
exercise therapy for, 184, 235,
243–253
mortality in, 188–192
NFkB pathway in, 199
obesity and, 184, 204–205, ix
Pravastatin for, 196, 201
prevalence of, 8, 184, 187, 193, vii
prognosis, 187, 206, 208, 211
risk factors for, 4, 86, 90–92,
183–188, 197–199, 205, vii
severe, 269–270, 278

- Simvastatin for, 195–197, 201, 204, 205, 234
smoking and, 10, 184, 185, 205–206, 236
symptoms of, 2–4, 24, 243–244
transcatheter therapies for, 260–261
treatment, 16, 194, 224, 258, vii, viii
Tricor (Fenofibrate) for, 195, 201, 204, 205, 234, 235
walking in, 4, 189–190, 192, 225
LpA. *See* Lipoprotein A (LpA)
L-TAP (Lipid-Treatment Assessment Project), 69
Lumbar stenosis and
 pseudoclaudication, 12
Lupus erythematosus and Raynaud's phenomenon, 14
LXRs and HDL metabolism, 146–147
Lymphocyte function-associated protein (LFA-1) in endothelial interactions, 114
Lysosomal acid lipase (LAL) and LpA, 141
- M**
- MAAS (Multicentre Anti-Atheroma Study), 64
Macrolide antibiotics and statins, 196–197
Magnetic resonance angiography (MRA)
 applications, 36–37
 contraindications, 37
 described, 36
Magnetic resonance imaging (MRI), 36, 37
MARS (Monitored Atherosclerosis Repression Study), 64, 66
Mast cell (MC) in atherosclerosis, 104
MCP-1 in monocyte recruitment, 114
MI. *See* Myocardial infarction (MI)
Microalbuminuria and atherosclerosis, 101
Milrinone, 228
Minnesota Regional Peripheral Artery Disease Screening Study, 237
Mitogens and atherosclerosis, 122–123
MMPs and vascular remodeling, 149, 150
Monitored Atherosclerosis Repression Study (MARS), 64, 66
Monocytes, 114, 115
Monounsaturated fatty acids (MUFAs) in atherosclerosis, 108–109
MRA. *See* Magnetic resonance angiography (MRA)
MRFIT (Multiple Risk Factor Intervention Trial), 90–92, 197
MRI. *See* Magnetic resonance imaging (MRI)
MUFAs (monounsaturated fatty acids), 108–109
Multicentre Anti-Atheroma Study (MAAS), 64
Multiple Risk Factor Intervention Trial (MRFIT), 90–92, 197
Myeloperoxide (MPO) in atheroma, 134
Myocardial infarction (MI) and homocysteine, 112
 indicators of, 189, 193
 preventing, 87, 89–90, 93–94, 203, 237
 risk factors for, 86, 91, 126, 187, 197
 treatment for, 207
- N**
- Nefazodone and statins, 196–197
Neopterin and angina, 115
Neurogenic claudication. *See* Pseudoclaudication
NFκB pathway
 in atherosclerosis, 117, 135
 in LEAD, 199

- Niacin**
 Advicor (lovastatin + niacin), 205, 235
 aspirin and, 204
 and atherosclerosis, 66–68
 complications, 202
 effects of, 201–208, 235
- Niaspan**, 202, 203
- Nicotine**. *See also* Smoking
 addiction to, 44–45, 206
 replacement therapy for, 47, 48, 231
 withdrawal symptoms, 44
- Nifedipine and statins**, 196–197
- Nisoldipine and statins**, 196–197
- Nitrous oxide (NO)**
 NOS, forms of, 105, 286
 production of, 104
- Nortriptyline for smoking**, 47
- O**
- Obesity**
 in atherosclerosis, 109–110
 and CVD, 86, 100
 and LEAD, 184, 204–205, ix
- Olive oil and inflammation**, 108–109
- Oncostatin M in calcification processes**, 151
- Optison (Albumin, sonicated)**, 192
- Osteoprotegerin (OSP) in CAD**, 150
- Oxidative stress in CAD**, 138
- oxLDL**
 atherogenicity of, 134
 in CAD, 115–116
 and dendritic cells, 117–118
 in ECs, 106
 function of, 114
 and monocytes, 136
 and proteoglycans, 148–149
- Oxygen uptake and CVD mortality**, 93
- P**
- P2 receptors, function of**, 104–105
- Palmaz stent**, 280
- Palm olein oil**, 109
- PARTNERS study**, 236
- Pathogens and cholesterol metabolism**, 118
- PDGF (Platelet-derived growth factor)**, 125–127
- Pentoxifylline**, 224–227
- Percutaneous transluminal angioplasty (PTA)**, 262–264
- Peripheral arterial disease (PAD)**
 anatomic distribution of, 54–55
 development of, 58
 and diabetes, 53–58
 and hypercholesteremia, 58, 63, 78, 81
 hyperlipidemia in, 61–70, 80
 and hypertension, 58, 75–81
 lipids, lowering, 67–69
 prevalence, 61
 prognosis, 57–58
 risk factors for, 55, 56, 79–81
 VEGF in, 103
- Persantine IV**, 190–192
- PG12 prostaglandin and atherosclerosis**, 151
- Phase contrast (PC) angiography described**, 36
- Phospholipid transfer protein (PLTP) as protective mechanism**, 139
- Photoplethysmography (PPG) technique for toe pressures**, 27
- Physician's Health Study**, 237
- Pima Indians and diabetes**, 55, 56
- Plaques**
 ACAT in, 139
 aortic calcified and CVD, 54–55
 classification of, 263
 DNA damage/repair in, 138
 formation of, 103, 105, 117, 120
 genome destabilization in, 121

- and inflammation, 113
 - rupture of, 104, 149
 - Plasminogen activator inhibitor (PAI-1) and plaque formation, 103, 117
 - Platelet-derived growth factor (PDGF), 125–127
 - Platelet factor 4 (PF4), function of, 104
 - Platelets, 104, 125–126. *See also* Antiplatelet therapy
 - Plavix (Clopidogrel), 193, 237
 - POBA (Plain old balloon angioplasty), 259, 265, 266, 279
 - Polyunsaturated fatty acids (PUFA) in CAD, 108
 - and cholesterol uptake, 147
 - peroxidation of, 133
 - PON and lipid oxidation, 145
 - Popliteal artery aneurysm and claudication, 10–11
 - POSCH (Program on the Surgical Control of Hyperlipidemias), 66, 68
 - Post Coronary Artery Bypass Graft trial, 65
 - PPARs and HDL metabolism, 147
 - PPG. *See* Photoplethysmography (PPG)
 - Pravastatin
 - for atherosclerosis, 65
 - for LEAD, 196, 201
 - LIPID (Long Term Intervention with Pravastatin in Ischemic Disease) study, 65
 - Probucol for atherosclerosis, 68
 - Probucol Quantitative Regression Swedish Trial (PQRST), 68
 - Progesterone in atherosclerosis, 130
 - Program on the Surgical Control of Hyperlipidemias (POSCH), 66, 68
 - Prospective Munster Cardiovascular Study, 198
 - Proteoglycans
 - in atherosclerotic lesions, 150
 - cytokines and, 148–149
 - and endothelial cells (ECs), 106
 - growth factors and, 148–149
 - lipids and, 148
 - oxLDL and, 148–149
 - Pseudoclaudication described, 11–13
 - PUFA. *See* Polyunsaturated fatty acids (PUFA)
 - Pulse volume recordings (PVRs), 25
- ## R
- Rampiril, 232
 - Rapamune, 265
 - Raynaud's phenomenon described, 10, 13–16
 - REGRESS (Regression Growth Evaluation Statin study), 65
 - Renal disease and diabetes, 53
 - Report on Smoking and Health*, 40
 - Resistance training as therapy, 247–248
 - Rest pain
 - described, 9–10
 - evaluating, 29, 34
 - Revascularization. *See also* Surgery and free tissue transfer, 277
 - indications for, 270–271
 - REVERSAL study, 196
 - Reverse cholesterol transport (RCT) described, 197–198, 204
 - Rosuvastatin, 201, 204, 235
 - Rottingham study, 110
- ## S
- Saint Thomas's Trial, 67
 - Salicylates for skin flushing, 202–204
 - Scandinavian Simvastatin Survival Study (4S), 64, 68–69
 - SCAT (Simvastatin/Enalapril Coronary Atherosclerosis Trial), 64

- Scleroderma and Raynaud's phenomenon, 14
 Seven Countries Study of CVD, 87–88
 Sex hormones in atherosclerosis, 129–131
 SHEP (Systolic Hypertension in the Elderly Program), 79, 187
 Simvastatin
 for atherosclerosis, 64, 68–69
 for LEAD, 195, 201, 204, 205, 234
 mortality in LEAD, reducing, 195–197
 Scandinavian Simvastatin Survival Study (4S), 64, 68–69
 SCAT (Simvastatin/Enalapril Coronary Atherosclerosis Trial), 64
 Vytorin, 201, 204
 Simvastatin/Enalapril Coronary Atherosclerosis Trial (SCAT), 64
 Single photon emission computed tomography (SPECT), 188–190
 Sirolimus, 265
 Sirolimus-Eluting stents, 265
 Sjogren's syndrome and Raynaud's phenomenon, 14
 Skin perfusion pressure measurements, taking, 27
 Smoking
 and atherosclerosis, 76, 78, 111–112, 231
 cessation
 benefits of, 43, 186, 205–206
 issues, 44–45
 programs, physician-delivered, 45–50
 and CVD risk, 40–43
 healthcare costs of, 40, 43
 health problems associated with, 39–42
 and LEAD, 10, 184, 185, 205–206, 236
 nicotine
 addiction to, 44–45, 206
 replacement therapy for, 47, 48, 231
 withdrawal symptoms, 44
 and PAD, 56, 81
 passive, 111–112
 rates, 44
 and Raynaud's phenomenon, 15
 relapse, preventing, 49
 treatment, medical, 43, 47
 Zyban (Bupropion SR, Welbutrin), 47, 48, 206, 231
 SPECT (Single photon emission computed tomography), 188–190
 Sphingomyelin and CAD, 131
 Spinal stenosis. *See* Lumbar stenosis and pseudoclaudication
 sPLA(2)-X in atherosclerosis, 145
 SR-B1 and cholesterol efflux, 144
 4S (Scandinavian Simvastatin Survival Study), 64, 68–69
 Statins. *See also individual drug by name*
 atherosclerosis and, 64–65
 benefits of, 197
 complications of, 196–197, 201
 fibrates and, 195, 234
 for MI, 206
 Stenosis
 arterial, diagnosis of, 28–35
 critical, 28, 30–35
 lumbar, 12
 treatment, 262–264
 Stents, 264–266, 279–283
 Stress
 in atherosclerosis, 101–102, 128–129
 echocardiography, 192–194
 in VSMCs, 138
 Stroke
 and alcohol, 110
 antiplatelet therapy for, 237

- diabetes and, 54
 - hypertension and, 77
 - risk factors for, 91, 116, 136, 187, 197
 - and smoking, 41, 42
 - Sulphonylureas and CVD, 100
 - Surgery, 257–267, 270–286. *See also individual procedure by name*
 - Sympathectomy, 277–283
 - Synthetic conduits, 274–275
 - Systolic Hypertension in the Elderly Program (SHEP), 79, 187
 - Systolic pressures, taking, 24–25
- T**
- Tangier disease, 144
 - TGF- β 1 (Tumor growth factor β 1), 140
 - TGF- β (Transforming growth factor β), 127
 - Thioredoxin as protective mechanism, 138
 - Thrombolysis, 265–266, 276
 - Thrombosis
 - described, 34
 - development of, 102–104, 136
 - formation and smoking, 42
 - Time of flight (TOF) angiography described, 36
 - Tissue factor pathway inhibitor (TFPI) and EC dysfunction, 102–103, 149
 - Tissue transglutaminase (tTG), function of, 103
 - Torcetrapib, 198
 - Trabia study of PAD, 81
 - TRAFFIC study, 229
 - Transcutaneous oximetry (TCPO2)
 - described, 26
 - Transforming growth factor β (TGF- β) n VSMCs, 127
 - Treadmill testing described, 27, 192
 - Trental (Pentoxifylline), 224–227
 - Tricor (Fenofibrate), 195, 201, 204, 205, 234, 235
 - Tumor growth factor β 1 (TGF- β 1), 140
 - Tumor necrosis factor α (TNF- α)
 - in calcification processes, 151
 - in inflammation, 114–115, 128
 - and insulin, 107
- U**
- Uncoupling protein 2 (UCP2) as protective mechanism, 139
 - United Kingdom Prospective Diabetes Study, 232
 - Urokinase, 265–266
- V**
- VAHIT (Veteran's Affairs High-Density Lipoprotein Intervention Trial), 66, 200
 - Valsartan, 233
 - Vascular claudication and pseudoclaudication, 12
 - Vascular endothelial growth factor (VEGF)
 - and angiogenesis, 286
 - for CAD/LEAD, 229
 - in endothelial cells, 106
 - and PAD, 103
 - Vascular smooth muscle cells (VSMCs)
 - growth factors in, 127
 - migration of, 126, 141
 - oxidative stress in, 138
 - PDGF in, 125, 126
 - phenotypes in, 120–122
 - STS expression levels, 130
 - Vasospastic claudication. *See* Raynaud's phenomenon
 - VEGF, Vascular endothelial growth factor (VEGF)
 - Veteran's Affairs Cooperative Study, 275–276

Veteran's Affairs High-Density
Lipoprotein Intervention Trial
(VAHIT), 66, 200

Vinca alkaloids and Raynaud's
phenomenon, 15

VSMCs. *See* Vascular smooth
muscle cells (VSMCs)

Vytorin (simvastatin + ezetimibe),
201, 204

W

Walking

and cilostazol, 228

distance, improving, 246, 247,
251–252

in LEAD, 4, 189–190, 192, 225

Welbutrin, 47, 48, 206, 231

West of Scotland Coronary
Prevention Study Group
(WOSCOPS), 63–64

WHO/Rose Questionnaire
described, 4, 5, 81

WOSCOPS (West of Scotland
Coronary Prevention Study
Group), 63–64

Y

Young patients, congenital lesions
in, 10

Z

Zetia (Ezetimibe), 201, 204, 235

Zyban (Bupropion SR, Welbutrin)
for smoking, 47, 48, 206, 231