CHAPTER 1

Anatomy, Physiology, and Response to Vascular Injury

Anthony C. DeFranco, Hongbao Ma, SriCharan C. Kantipudi, and George S. Abela

Key Points

- Arteries have two major properties: elasticity and contractility. The elastic recoil of arteries forces blood forward.
- Normal endothelial function includes a barrier to prevent thrombosis and production of vasoreactive substances.
- Arterial remodeling is an adaptive change in the vessel lumen area that increases lumen size to accommodate atheroma (positive remodeling) or scars down the arterial lumen (negative remodeling).
- Increase in arterial flow stimulates nitric oxide production and enhances vascular dilation.
- Lipid challenges may interfere with normal vascular tone regulation.
- Brachial artery reactivity can be used to evaluate the status of vascular tone and may eventually serve to risk-stratify patients for future cardiovascular events.

INTRODUCTION

Understanding the anatomy and physiology of the arterial system is critical to understanding vascular disease processes and the therapeutic interventions used to address the altered functions. This chapter connects this basic knowledge to the response to injury, the repair of the vascular system, and the complex autocrine and paracrine dynamics that regulate the arterial circulation.

BASIC GROSS ANATOMY OF THE PERIPHERAL ARTERIAL CIRCULATION

Blood vessels form a network of tubes that transport blood from the heart to the tissues of the body and then return it to the heart (1). This was first described by William Harvey in 1628 (2). Arteries are vessels that carry blood from the heart to the tissues. Large, elastic arteries leave the heart and divide into medium-size muscular arteries, which branch out into the various regions of the body. Medium-size arteries then divide into small arteries, which divide into smaller arteries and arterioles. In the tissues, the arterioles branch into countless microscopic vessels called capillaries. Through the walls of the capillaries, substances such as O_2/CO_2 and nutrient/waste are exchanged between the blood and body tissues. In the tissues, some capillaries reunite to form small veins called venules. The venules merge to form progressively larger veins. The veins deliver blood from tissue back to the heart. Because blood vessels also require O_2 and nutrients, they also have blood vessels in their walls, called vaso vasora.

Human arterial circulatory routes are shown in Fig. 1.1. The principal human veins are shown in Fig. 1.2.

Three arteries originate from the aortic arch: the brachiocephalic, which supplies part of the neck, head, brain, and right arm; the left common carotid, which supplies part of the neck, head, and brain; and the left subclavian, which supplies the left arm. The brachiocephalic divides into the right subclavian and the right common carotid arteries. The right subclavian gives rise to the right vertebral artery, and the left subclavian gives rise to the left vertebral artery. The continuation of the subclavian into the axilla is called the axillary artery, which continues into the arm as the brachial

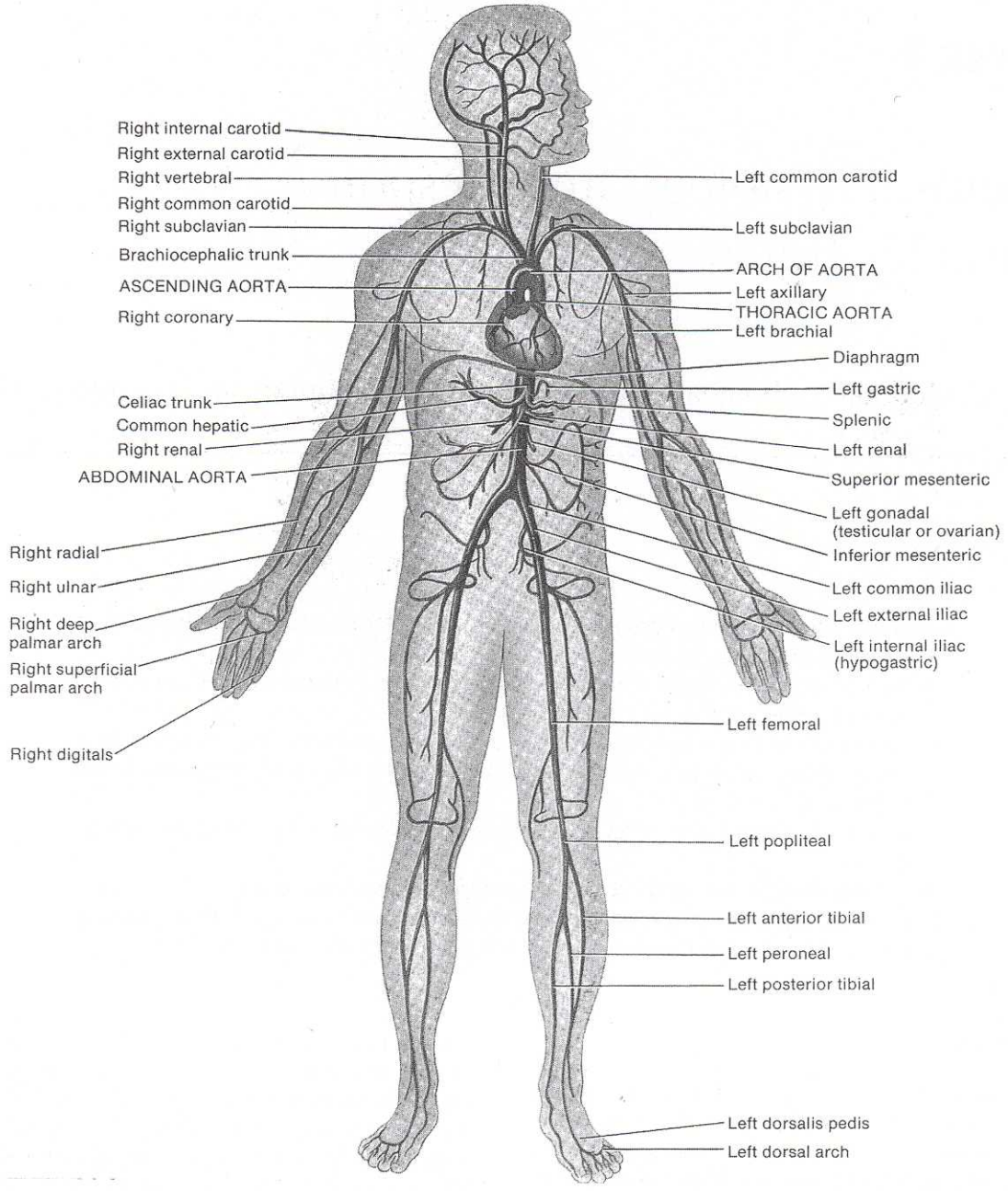

FIG. 1.1. Human arterial circulation including cerebral area, neck, torso, arms, and legs. (From Tortora GJ, Anagnostakos NP. *Principles of anatomy and physiology,* 6th ed. New York: Harper & Row, 1990, p. 498, with permission.)

artery, then divides into medial ulnar and lateral radial arteries, which go to the arm and the fingers.

The right and left common carotid arteries pass upward into the neck. These divide into the external and internal carotid arteries. The external carotids supply blood to the thyroid gland, tongue, face, throat, ear, scalp, and dura mater. The internal carotids supply blood to the brain, eyes, forehead, and nose.

The aorta continues after a downward turn (descending aorta) and enters the abdomen through the diaphragm. The vessel becomes the abdominal aorta, which travels in the retroperitoneal space, and at the mid-abdominal level it forks into the right and left common iliac arteries. Before it branches, it gives rise to the celiac, superior, and inferior mesenteric arteries and the spinal artery.

Each of the two common iliac vessels further divides into internal and external iliac arteries. The internal iliac arteries provide blood to the pelvis, including parts of the rectum, the sexual organs, and the buttocks. The external iliac arteries provide blood to the legs. The external iliac turns into the femoral artery, which further splits into superficial and deep femoral arteries. The superficial femoral artery

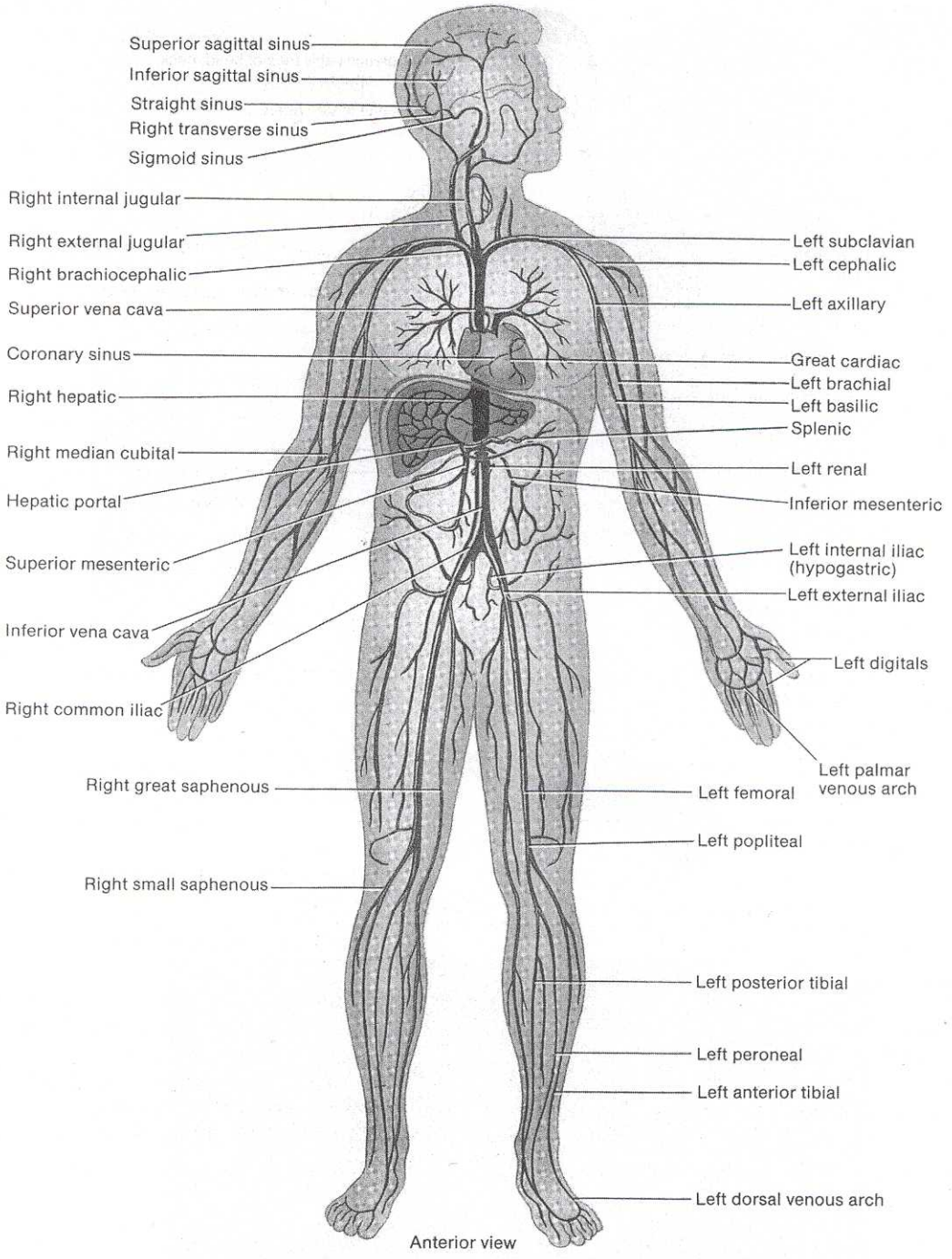

FIG. 1.2. Human venous circulation including cerebral, area neck, torso, arms, and legs. (From Tortora GJ, Anagnostakos NP. *Principles of anatomy and physiology,* 6th ed. New York: Harper & Row, 1990, p. 503, with permission.)

continues above the knee to form the popliteal artery. The popliteal spans the knee joint. In the lower leg, the popliteal becomes the tibioperoneal trunk, whose branches further supply the ankle and the foot via the posterior tibial and dorsalis pedis arteries (3).

The venous structures generally parallel the arterial structures. Smaller vessels in the periphery begin the long trek back to the heart and the lungs. The vessels of the head and the upper part of the body empty into the superior vena cava; the vessels of the lower half of the body empty into the inferior vena cava. The inferior and superior vena cavae empty into the right atrium, which completes the vascular circuit back to the heart (4).

HISTOLOGY OF ARTERIES AND VEINS

Arteries have walls constructed of three coats or tunics and a hollow core (lumen) through which blood flows (5). The

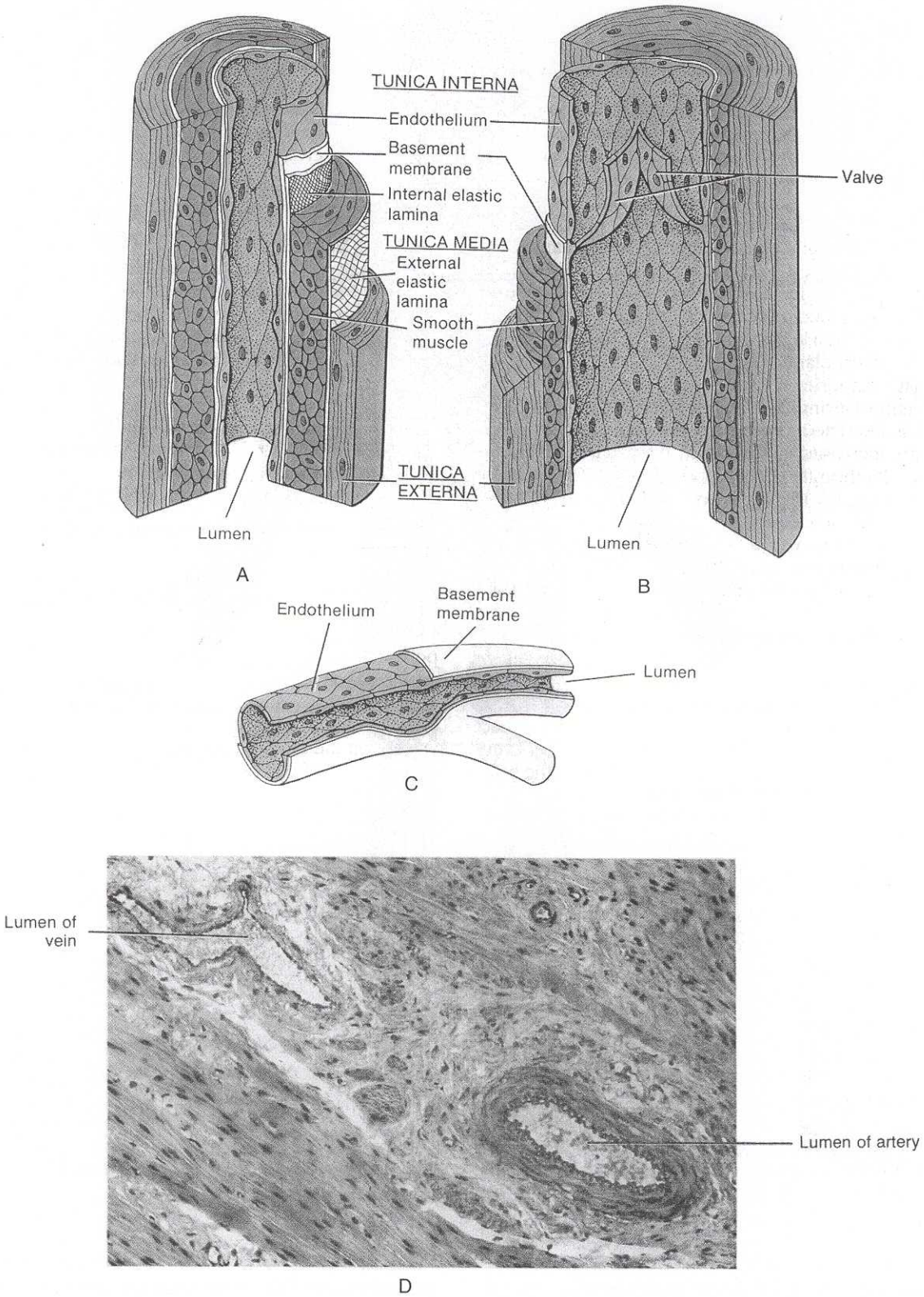

FIG. 1.3. Basic structure of artery, vein, and capillary. **A:** Artery, demonstrating various layers. **B:** Vein, demonstrating various layers. **C:** Capillary. **D:** Histologic cross section of artery (*right*) and vein (*left*) demonstrating differences in wall thickness between the two vessels. (From Tortora GJ, Anagnostakos, NP. *Principles of anatomy and physiology,* 6th ed. New York: Harper & Row, 1990, p. 607, with permission & courtesy of Andrew Kuntzman.)

inner coat of an arterial wall (the tunica interna) is composed of a lining of endothelium, which is in contact with the blood; a basement membrane; and a layer of elastic tissue called the internal elastic lamina. The middle coat (tunica media) is usually the thickest layer and consists of smooth muscle as well as collagenous and elastic fibers. The outer coat (tunica externa) is composed principally of elastic and collagenous fibers. An external elastic lamina may separate the tunica externa from the tunica media (Fig. 1.3).

Arteries have two major properties: elasticity and contractility. When the ventricles contract and eject blood into the large arteries, the arteries expand to accommodate the extra blood. Then, as the ventricles relax, the elastic recoil of the arteries forces the blood onward. The contractility of the artery comes from its smooth muscle cells.

The large arteries (elastic arteries) include the aorta and the brachiocephalic, common carotid, subclavian, vertebral, and common iliac arteries. The wall of elastic arteries is relatively thin and its tunica media contains more elastic fibers and fewer smooth muscle cells.

The medium-size arteries (muscular arteries) include the axillary, brachial, radial, intercostal, splenic, mesenteric, femoral, popliteal, and tibial arteries. Their tunica media contains more smooth muscle than elastic fibers and they are more important to the vasoconstriction and vasodilation involved in adjusting the flow of blood.

Ananastomoses are junctions of two or more vessels supplying the same body region. They give alternate routes for the blood to flow to a body part.

The exchange of nutrients and wastes between the blood and tissue cells occurs in capillary arteries. Capillary walls are composed of a single layer of endothelium cells and a basement membrane, which facilitate the exchange of substances.

Several capillaries unite to form small veins called venules. Venules collect blood from capillaries and drain it into veins. Veins are composed of essentially the same three types of coats as the arteries. The vein tunica interna and media are thinner and the tunica externa is thicker than those of accompanying arteries (6).

PHYSIOLOGY

Endothelium

Normal endothelial function is important in maintaining homeostasis. In addition to functioning as a physical and physiological barrier to prevent thrombotic and vasoactive substances from coming into contact with underlying smooth muscle cells, the endothelium possesses two crucial functions: as a secretory tissue and as an antithrombotic surface.

Endothelial Cell Function as a Secretory Tissue

Since Furchgott described the role of the endothelium in the relaxation of the vessel wall in response to acetylcholine in terms of a "substance" later called endothelial-derived relaxation factor, there have been important contributions by other investigators that have led to further understanding of the function of the endothelium (7,8).

In the secretory role, endothelial cells synthesize important vasoactive substances including endothelial-derived relaxation factor (EDRF), endothelial-derived hyperpolarizing factor (EDHF) (9), and prostacyclin, which act as vasodilators; and endothelin and endothelial-derived contracting factor (EDCF), which act as vasoconstrictors. Biological and chemical evidence supports the proposal that nitric oxide (NO), a potent vasodilator is a form of EDRF (10). Endothelial cells also make substances involved in the coagulation pathways, which include factor VIII antigen, von Willebrand's factor, and plasminogen activator. In addition, they produce collagen, elastin, glycosaminoglycans, and fibronectin, which are structural components of extracellular matrix (11). The endothelium manufactures and secretes heparan sulfates and growth factors, which regulate the smooth muscle cells. It also modifies the extracellular matrix by production of matrix metalloproteinases.

Endothelial cells regulate the metabolism of the plasma lipids. They bind the lipoprotein lipase by the heparin sulfates, and play a role in the transport and metabolism of low-density lipoprotein (LDL) and chylomicrons and release of free fatty acids. They possess receptors for LDL and thereby modify it (12). Normally the endothelial monolayer downregulates the LDL receptors. However, in a diseased state, the endothelium can facilitate the uptake of the LDL, leading to an increase in the cholesterol esters in the vessel wall. It clears and alters adenine nucleotides, nucleosides, bradykinin, angiotensin I, catecholamines, and serotonin in the circulation.

Role of Endothelium in the Thrombotic and Antithrombotic Balance

The negative charge on the surface of normal endothelial cells contributes to the antithrombotic surface, which prevents platelet adhesion and activation and resists coagulation. However, the same cells, when stimulated, can manufacture and secrete prothrombotic agents. Thus, the endothelium regulates a functional thrombosis/antithrombosis–thrombolytic balance.

On one hand, the endothelium produces prostacyclin, which inhibits platelet aggregation (13), and thrombomodulin, which activates protein C. The activated protein C inhibits plasminogen activator inhibitor-1 (PAI-1) and interacts with protein S to inactivate the activated factors V and VIII to limit thrombosis. Heparin-like molecules secreted by the endothelium adhere to anti-thrombin III to clear the thrombin. Another important function of the endothelium is to elaborate the tissue plasminogen activator, which enhances clot lysis. On the other hand, under inflammatory conditions, the endothelium can become potently prothrombotic. This is accomplished by an increase in expression of the tissue factor (14) and leukocyte adhesion molecules on the surface and a

decrease in expression of thrombomodulin. Tissue factor activates the factors VII, IX, and X. Activated Xa assembles the prothrombinase complex, releasing thrombin, which in turn stimulates von Willebrand's factor, which, along with thrombospondin and fibronectin, furthers the thrombotic process.

Vascular Smooth Muscle

The smooth muscle cells contract and relax the arterial wall in response to hormonal stimulation and the endothelial cells. The vasoconstriction is facilitated by second-messenger pathways, which include G proteins. Growth factors such as platelet-derived growth factor (PDRF) activate similar signaling pathways. The cell growth takes place in two forms. Hypertrophy can occur in response to angiotensin II and thrombin and in large vessels due to hypertension. Hyperplasia can occur in response to growth factors like PDRF and fibroblast growth factor (FGF) after vascular injury.

Interaction of Endothelium with Vascular Smooth Cells

Endothelial cells play a dual role in the regulation of vascular tone.

Endothelial-Derived Relaxation Factor

In 1980, Furchgott first described the dilation of rabbit aortic rings in response to acetylcholine in the presence of the intact endothelium (7,8). The NO, which is believed to be the predominant form of EDRF, is synthesized from L-arginine by the enzymatic action of NO synthase. NO is unstable and has a mechanism of action different than that of prostaglandins, and is inhibited by methylene blue and oxygen free radicals. NO crosses the smooth muscle cell membrane and binds to the guanylate cyclase and increases the formation of cyclic GMP, which in turn reduces the intracellular calcium concentration, thereby causing dephosphorylation of the myosin light chain and ultimately relaxation (15). Other factors that can cause the release of EDRF by increasing the intracellular calcium concentration are norepinephrine, thrombin, ATP, bradykinin, vasopressin, ionophores, serotonin, histamine, and fatty acids.

Adenosine

Adenosine activates cAMP to relax the smooth muscle by binding to purinergic P1 receptors. Adenosine nucleotides (ADP and ATP) bind to P2 receptors and have a dual role. They stimulate the endothelial P2 receptors to release EDRF and prostacyclin, and act on P2 receptors on vascular smooth muscle to cause vasoconstriction. However, the endothelium can regulate these functions by converting ADP or ATP into adenosine through the ectonucleotidase enzymatic system.

Prostacyclin

Prostacyclin is produced by the endothelium and relaxes the vascular smooth muscle by increasing the levels of intracellular cAMP. It also works as a platelet suppressant and antithrombotic agent. Other factors that stimulate the synthesis of prostacyclin are PDGF, bradykinin, substance P, adenine nucleotides, and epidermal growth factor.

Endothelin

Endothelins occur in three types, of which endothelin-1 is the most potent vasoconstrictor. They work by the activation of phosphoinositide/protein kinase signaling pathway and play a role in nitroglycerin tolerance and as chemoattractants for monocytes.

Angiotensin-Converting Enzyme

Angiotensin-converting enzyme (ACE) is a protein expressed on the surface of endothelium, and converts angiotensin I to the potent vasoconstrictor angiotensin II and also deactivates bradykinin.

Regulation of Smooth Muscle Cell Growth

Even though the endothelium plays a dual role, its net effect is growth inhibitory. Two possible mechanisms are hypothesized on how the endothelium exerts a tonic inhibitory influence on smooth muscle cell growth. In one, it works as a physical barrier preventing blood-borne growth factors from coming into contact with underlying smooth muscle. The second mechanism is by secretion of growth-inhibiting factors like EDRF, heparin, heparin sulfates, and transforming growth factor-1. The growth factors eluted by endothelium are platelet-derived growth factor, interleukin-1, fibroblast growth factor, insulin-like growth factor-1, and endothelin.

Hemodynamic Influences on the Endothelium

Langille first showed that endothelium is essential for the compensatory arterial response to long-term changes in luminal blood flow rates (16). Shear stress, stretch of the vessel wall, and elevated pressure independently affect endothelial function and morphology.

RESPONSE TO VASCULAR INJURY

Arterial Remodeling

Remodeling is defined as a change in vessel area (i.e., within the external elastic membrane [EEM]) as atherosclerosis develops. Positive remodeling occurs when the area within the EEM area increases as atheroma develops. Glagov and colleagues first described these phenomena in peripheral specimens and then in coronary specimens in necropsy studies (17); subsequent intravascular ultrasound (IVUS) studies corroborated these observations in coronary (18–20) and peripheral arteries (21) *in vivo*. In positively remodeled segments, Glagov hypothesized that vessel expansion is "compensatory" because lumen size was relatively preserved

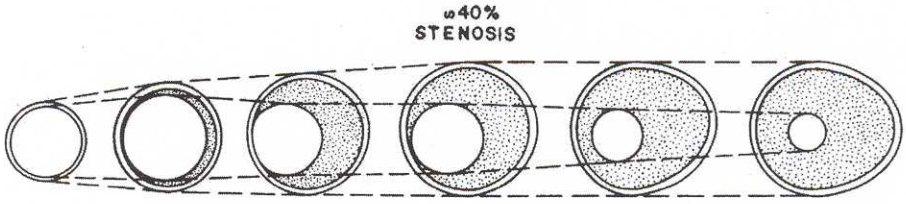

FIG. 1.4. The concept of vascular remodeling in atherosclerotic arteries is demonstrated sequentially in response to enlarging atherosclerotic plaques. In the early stages of plaque deposition, the lumen remains normal or enlarges slightly (*left*). When intimal plaque enlarges to involve the entire circumference of the vessel and produces more than 40% stenosis, the artery is no longer able to enlarge at a rate sufficient to prevent narrowing of the lumen. This leads to encroachment of the lumen. (From Glagov S, Weisenberg E, Zarms C, et al. Compensatory enlargement of human atherosclerotic coronary arteries. *N Engl J Med.* 1987;316:1371–1375, with permission.)

despite considerable amounts of atheroma compared to more normal segments in the same vessel. However, beyond a certain limit, in the range of 30% to 50% cross-sectional narrowing, this "compensatory" mechanism fails and luminal dimensions become progressively compromised, and hemodynamically significant obstruction occurs (Figs. 1.4 and 1.5).

Recently, histopathologic and IVUS studies have demonstrated that in *de novo* coronary lesions, remodeling can be negative as well as positive. At negatively remodeled sites, the cross-sectional area (CSA) within the external elastic lamina is significantly less than at an appropriate reference segment. Thus, at some sites in the peripheral (22) and coronary (23) circulations, stenoses are due to both atheroma accumulation and a decrease in the total vessel area.

Although the biological mechanisms responsible for positive and negative remodeling are unknown, the remodeling phenomenon has several critical implications. First, remodeling can conceal substantial atherosclerotic plaque burden even in the presence of angiographically normal coronary and peripheral vessels. Second, because of this, most contemporary studies of regression or stabilization of atherosclerosis use some modality that can accurately measure the effects of the intervention on remodeled segments, such as intravascular ultrasound or carotid B-mode ultrasound. Regression of disease, discussed later, may be a potential therapeutic strategy; however, studies designed to test whether arterial remodeling can be favorably affected are still in progress (24).

VASOREACTIVITY OF THE PERIPHERAL VASCULATURE

Vasoresponse of Normal Peripheral Endothelium

In the last decade, our understanding of the vascular biology of the human arterial system has experienced a fundamental paradigm shift in the concepts of arterial function and pathophysiology (Table 1.1). Arteries are no longer considered to be passive, fixed conduits that merely distribute blood to end organs. Instead, it is now recognized that the arterial system is

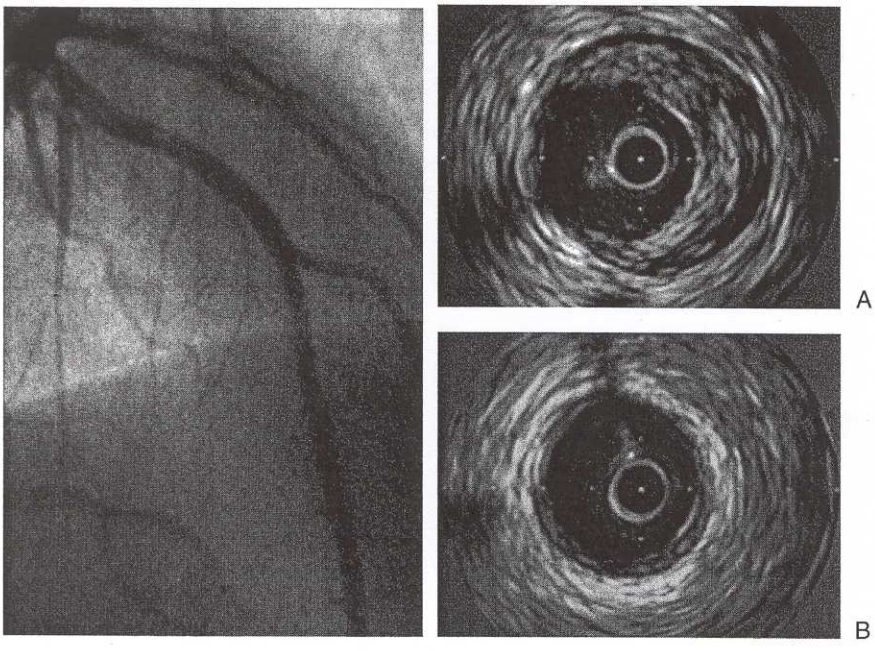

FIG. 1.5. Example of arterial remodeling illustrated by intravascular ultrasound in the coronary circulation. The external elastic membrane (EEM) cross-sectional area of the angiographically normal reference site **(A)** is nearly 50% larger than the EEM area of the distal site **(B),** yet the lumen size is the same. Thus, there has been "expansion" or "compensatory remodeling" that has accommodated to the atheroma mass.

TABLE 1.1. *Factors affecting blood supply and symptoms in peripheral arterial disease*

Flow-limiting lesions ("fixed" stenoses, long lesions, tandem/multiple lesions, etc.)
Presence and extent of collateral circulation
Endothelial function/vasodilator reserve
Metabolic activity of the supplied territory
Impaired response to exogenous vasodilators
Enhanced vasoconstriction (serotonin, endothelin, angiotensin II, thromboxane)
Abnormal rheology
Reduced red blood cell distensibility
Increased leukocyte adhesion to the vessel wall
Increased platelet adhesion and aggregation
Increased fibrinogen levels
Acute vascular injury/plaque rupture
Thrombosis, embolization

a complex biomechanical system that responds dynamically to metabolic, biochemical, and hemodynamic changes in its local environment and that of the downstream tissues that it perfuses. The arterial endothelium is the largest paracrine organ in the body; it secretes many factors that regulate vascular tone, leukocyte and platelet interaction, thrombogenicity, lipid metabolism, and cell growth. Cell membrane receptors enable the endothelium to respond to an enormous number of external and internal stimuli; by means of these receptors, complex signal transduction mechanisms lead to the release of substances that regulate arterial constriction and dilation, thromboregulatory functions, and growth factors, which affect the arterial smooth muscle cells. The current paradigm of atherosclerosis considers that dysfunction of these processes contributes to or is the cause of the development of hypertension and atherosclerosis and exacerbates cardiac causes of heart failure.

Human arteries respond to physical and chemical stimuli to regulate arterial tone and adjust blood flow and distribution according to changes in the local environment. An increase in flow results in increased shear stress; shear results in an increase in endothelial release of NO, which causes acute vasodilation. This process is referred to as flow-mediated dilation (FMD). The exact mechanisms by which the endothelium senses and responds to acute changes in shear stress are the subject of intense investigation. The current working hypothesis is that acute (millisecond) changes in shear stress activate calcium-sensitive ionic channels in the endothelial cell membrane. These channels open in response to shear, hyperpolarize the cell membrane, augment the influx of calcium, and activate endothelial NO synthase (eNOS) (25–27). The result is an increase in the generation of NO and in FMD (28,29). This working hypothesis is supported by the observation that administration of an NO synthase (NOS) inhibitor or endothelial denudation abolishes FMD. Over longer time frames (minutes), shear stress induces phosphorylation of the eNOS enzyme, which results in an increase in its activity, generating higher net production of NO. Over even longer time periods, sustained or repeated shear stress (such as with a regular exercise program of adequate intensity) may induce increased eNOS gene transcription, which increases the capability of the endothelium to generate NO. Thus, over the long term, arteries also adapt to chronic changes in local and regional hemodynamic stresses and to systemic conditions in an attempt to preserve optimal cross-sectional area, biomechanical characteristics, and optimal blood flow to downstream tissues. This observation is already influencing strategies to alleviate symptoms and reduce complications in patients with peripheral arterial disease, as is discussed later. In addition to NO, other mediators may also play a role in this response, such as prostanoids (30) or the as-yet-unidentified endothelium-derived hyperpolarizing factor.

Angiography has been the gold standard for the serial assessment of peripheral arterial disease and it remains a vital tool for clinical diagnosis and management; however, there are two fundamental limitations that impair its ability to accurately assess the relationship between disease severity and end-organ perfusion. First, although a flow-limiting stenosis is often the most important determinant of insufficient blood supply, stenosis severity is a relatively insensitive measure of the ability of the vessel to deliver blood to distal tissues. Conventionally, a 50%-diameter stenosis or a 75%-area stenosis has been the cutoff for a "hemodynamically significant" lesion, but this concept is now recognized to be overly simplistic and physiologically inaccurate. The impact of a particular lesion that extends into the arterial lumen depends on many factors, including the length of the lesion, the size and metabolic activity of the downstream tissues, the presence or absence of collateral flow and disease in other vessels, and, most importantly for this discussion, the endothelial function of the entire arterial territory. Even by the 1970s several important deficiencies of angiography were apparent. Studies documented high interobserver variability of angiogram interpretation (31). Major discrepancies were observed between the apparent severities of lesions as observed by angiograms and those observed histologically at postmortem (32–34). Angiography cannot visualize structures less than 0.2 mm, even though clinically relevant calcifications or thrombi may be of this size.

Second, even though angiographically visible stenoses are often the most important determinants of blood supply to downstream tissues, functional abnormalities in vasoreactivity may also adversely affect blood flow and transform an asymptomatic patient into a symptomatic one. Patients with peripheral arterial disease have impaired vasodilator reserve in both conduit and resistance vessels, as is discussed later. The immediate (millisecond to millisecond), intermediate (minute to minute), and long-term changes in arterial tone and thus lumen area are often below the level of sensitivity for quantitative angiography to detect any change in arterial caliber.

Direct measurements of coronary and peripheral arterial flow are accurate and have provided important insights into arterial physiology. The agent used most commonly to assess endothelial function is acetylcholine (Ach) infused at

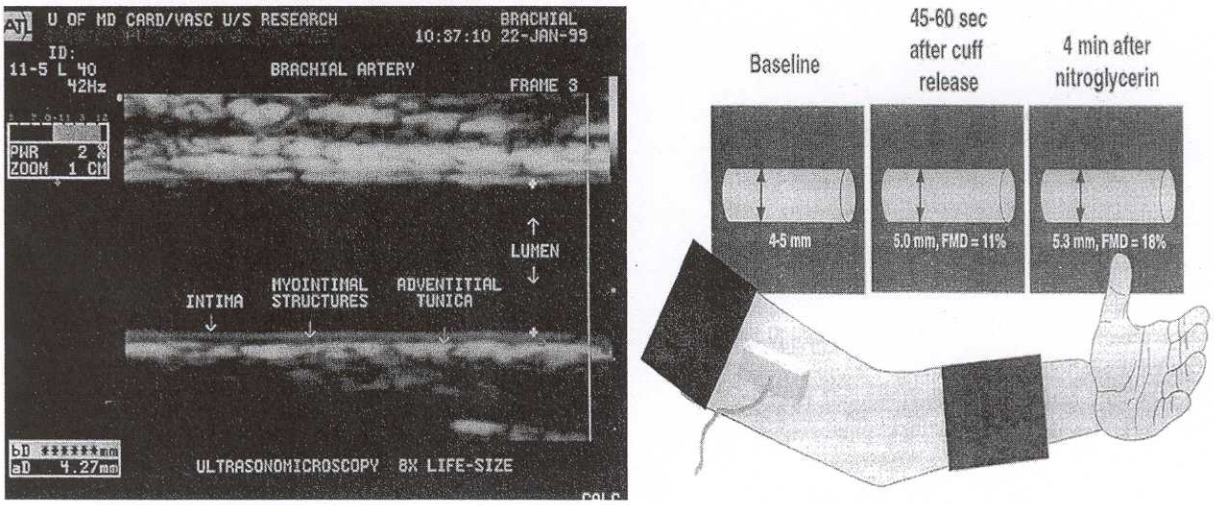

FIG. 1.6. Brachial artery reactivity study in a patient. Example of an ultrasound image obtained in the brachial fossa at baseline. (From Corretti MC, Anderson TJ, Benjamin EJ, et al. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. *J Am Coll Cardiol* 2002;39(2):257–265, with permission.)

doses of 10^{-8} to 10^{-6} mol per L. In normal arteries, Ach causes the release of NO and results in vasodilation. However, in atherosclerotic vessels, Ach induces vasoconstriction. Atherosclerosis is associated with reduced NO release (35,36) (and perhaps increased NO degradation). The mechanism of this paradoxical vasoconstriction is thought to be smooth muscle cell activation, because in the presence of lower levels of NO, Ach exerts a greater net activation of smooth muscles cells in the arterial media via muscarinic receptors.

Early noninvasive studies of peripheral endothelial function (some of which are cited in what follows) utilized plethysmography. In this technique, the technician places pneumatic cuffs at the wrist and the upper arm and a strain gauge around the forearm of the patient. The wrist cuff is inflated to 200 mm Hg to prevent blood flow to the hand, the upper arm cuff is inflated to 40 mm Hg, and the resulting venous occlusion and forearm engorgement are recorded on the plethysmograph as a measure of resting blood flow. The upper arm cuff is inflated above systolic pressure for 5 to 10 minutes, and repeat measurements after deflation are used to estimate hyperemic blood flow. As one might expect, this technique is cumbersome and is now less commonly used than measurement of brachial artery reactivity.

Brachial Artery Reactivity Testing

Although invasive studies continue to provide invaluable data on arterial physiology, these tests are impractical for serial studies. A noninvasive test, brachial artery reactivity (BAR), has been developed as a surrogate. The advantages of this methodology are that it is simple, noninvasive, and practical for serial studies. A two-dimensional ultrasound image of the brachial artery is acquired in a longitudinal plane above the antecubital fossa to allow accurate measurement of arterial diameter (Fig. 1.6). Skill and experience are required to select an image with clear definition of the anterior and posterior intimal interfaces of the lumen and the vessel wall during two-dimensioanl gray-scale imaging. Perivascular landmarks, such as veins and other structures, are used to maintain the same image location throughout the study. Time-averaging of the pulsed Doppler velocity signal allows estimation of basal blood flow. After baseline image acquisition, a blood pressure cuff is inflated either on the forearm or in the antecubital fossa to greater than 50 mm Hg above resting systolic pressure to occlude flow, typically for 5 minutes. The resulting downstream ischemia results in dilation of resistance vessels. When the cuff is deflated, this downstream vasodilation induces a high-flow state in the brachial artery, termed reactive hyperemia, and the resulting increase in shear stress causes brachial artery dilation. After cuff deflation, continuous two-dimensional longitudinal images are recorded for 1 to 2 minutes along with pulsed Doppler time-averaging of the mid-artery signal from the release of the blood pressure cuff for 15 seconds. Endothelial function can also be evaluated in the distribution of the femoral artery with a similar technique.

In individual with normal endothelial function, the brachial artery begins to dilate immediately after cuff deflation due to the increased velocity of blood flow and the increase in shear stress. Several studies suggest that the maximal increase in brachial artery diameter occurs 45 to 60 seconds after release (37–39). This response is dependent on endothelial production of nitric oxide, because studies document that it can be abolished after administration of NG-monomethyl-L-arginine (L-NMMA), a potent inhibitor of nitric oxide synthase (40,41). Flow-mediated vasodilation is usually reported as a percentage change in the poststimulus diameter

compared to baseline. Celermajer et al. reported a mean flow-mediated dilation of approximately 10% in individuals between the ages of 8 and 57 years of age (42). The International Brachial Artery Reactivity Task Force recommends that baseline diameter and absolute change should also be reported (43). In some studies, data on the degree of brachial artery dilation are supplemented with additional endpoints, such as the time and duration of vasodilator response (44,45). In subjects with abnormal endothelial function, flow-mediated dilation is impaired or absent, as discussed later.

Although simple in concept, there are many technical and physiological aspects of the procedure that affect its accuracy and reproducibility. The International Brachial Artery Reactivity Task Force has recently published a set of guidelines in an attempt to standardize the technical aspects of the procedure (43). There are many variables that the operator must control. First, many variables affect flow-mediated dilation. The patient must fast for at least 8 to 12 hours before study; caffeine, tobacco, high-fat foods, and some vitamins affect the results. Sympathetic stimuli can profoundly affect the results; thus, patients must be studied in a quiet, temperature-controlled room. The task force recommends that vasoactive medications be withheld for a minimum of four half-lives. Even the patient's menstrual cycle can affect the results (46). Second, the ultrasound equipment utilized must be optimal; broad-band (7 to 12 MHz) linear-array transducers and a high-resolution scanner are optimal. Third, measurements must be electrocardiogram-gated. Fourth, the technician performing the procedure needs to have considerable facility and experience with the procedure because the time window for data acquisition after cuff deflation is very brief. Although occlusion above the brachial fossa elicits a greater reactive hyperemic response (enhanced dilation of the brachial artery, perhaps by recruitment of a larger number of resistance vessels downstream) and is the preferred technique, it is technically more challenging due to the resulting distortion of the brachial artery and more difficult ultrasonic imaging (38). If serial testing before and after challenge with an exogenous agent is part of the study protocol, at least 10 minutes between the baseline and the postchallenge study is required to reestablish baseline physiology. Despite these and other technical challenges, in experienced laboratories the accuracy, reproducibility, and safety of this technique are well established (47). Recently developed commercially available systems offer the promise of standardization and greater ease of use.

Vasoresponse of Abnormal Endothelium

Endothelial Function in Preclinical Vascular Disease

Even in the earliest phases of atherosclerosis, there is often endothelial dysfunction. Whether endothelial function is the result of atherosclerosis or its cause (or whether the two are interdependent) is a subject of much research. Endothelial dysfunction associated with vascular injury has been proposed as a precursor to atherosclerosis (48). Impaired endothelial function can be demonstrated in asymptomatic children and young adults who have risk factors for atherosclerosis, such as hypercholesterolemia and smoking (42). Accordingly, tests of endothelial function are in development to diagnose early disease and to monitor response to interventions, such as risk factor modification. Atherosclerotic vessels have abnormal flow-mediated dilation, which is associated with atherosclerotic risk factors and is thought to be a marker of preclinical disease (42,49). The end result is that these arteries vasoconstrict in response to stimuli that in normal arteries are vasodilatory, and, conversely, may dilate at times when vasoconstriction is the appropriate physiological response.

Recent necropsy and intravascular ultrasound studies document that atherosclerosis is present in a substantial percentage of children and young adults. Autopsy data from Korean and Vietnam War victims documented that advanced atherosclerotic lesions (greater than 50% stenosis) were present in approximately 20% of soldiers who died at an average age of less than 25 years (50). Stary reported from another necropsy series that 65% of children aged 12 to 14 years had the earliest signs of atherosclerosis (51). The Bogalusa Heart Study examined a large number of subjects who died of nonvascular causes at less than 40 years of age; this study documented a high prevalence of atherosclerosis in these young and middle-aged individuals (52). In an intravascular ultrasound study of transplanted hearts at the Cleveland Clinic Foundation, Tuzcu and colleagues corroborated these necropsy findings. Fifty-two percent of coronary arteries from asymptomatic teenagers and young adults (mean age 33.4 years) had atherosclerotic lesions (53). Thus, there is overwhelming evidence that the earliest morphological changes of atherosclerosis occur in young individuals.

Although there are few data correlating endothelial function in young individuals with documented vascular disease (either by invasive or noninvasive methodologies, such as electron beam tomography, carotid intima–media thickness, or magnetic resonance angiography), the Bogalusa Heart Study demonstrated a strong correlation between morphological changes of atherosclerosis with conventional atherosclerotic risk factors as assessed postmortem (52). Thus, it is not surprising that in middle-aged individuals with atherosclerotic risk factors or established vascular disease, endothelial dysfunction as assessed by brachial artery reactivity is common.

As a result of these observations, there is intense interest in determining whether brachial artery reactivity testing can be used as a screening tool to identify people with preclinical coronary and peripheral atherosclerosis to target risk factor intervention and reduce subsequent vascular events. In patients with coronary disease, several studies suggest that endothelial dysfunction is an independent predictor of subsequent cardiovascular events (54,55). In a pilot study, Schroeder and colleagues examined 122 consecutive participants with suspected coronary artery disease (CAD) by history followed by exercise stress testing and cardiac

catheterization (56). One hundred and one patients had angiographic abnormality confirming the presence of disease; flow-mediated dilation was significantly higher in the group without than in the group with angiographic disease ($7.0 \pm 3.5\%$ vs. $3.8 \pm 4.1\%$, $p < 0.001$), for a sensitivity and specificity of 71% and 81%, respectively. However, the magnitude of the FMD abnormality did not discriminate the severity of the angiographic disease, and because IVUS studies have confirmed that some patients may have substantial atheroma burden in the absence of any angiographic abnormality, and coronary endothelial function was not assessed, some of the patients with angina but normal angiograms might still have had angina on the basis of endothelial dysfunction. Although BAR holds promise as a screening technique for the identification of vascular disease patients in the earliest stages of disease, this strategy requires more study before clinical application is appropriate. Brachial artery reactivity has also been suggested as a screening tool to identify the effect of various interventions on endothelial function, on the assumption that improvements might predict clinical improvement or a reduction in vascular events when such agents are tested in larger, subsequent trials powered for clinical endpoints (57).

Effect of Vascular Risk Factors on Peripheral Endothelial Function

Conventional atheroscleotic risk factors appear to increase the incidence of endothelial dysfunction. All conventional risk factors increase the oxidative stress on arterial endothelium, and the resulting increase in reactive oxygen species accelerates the degradation of nitric oxide. In a study of 500 individuals aged 5 to 73 years without known vascular disease, FMD was lower in the presence of hypercholesterolemia, smoking, hypertension, and a family history of premature vascular disease (58). An association between essential hypertension and endothelial dysfunction has been documented (59,60), suggesting the possibility that some abnormality of endothelial function may be the cause, rather than the result, of hypertension. Other studies have supported the association of uncontrolled vascular risk factors and an increased incidence of abnormal endothelial function using FMD techniques in either the brachial or the femoral distribution (61,62). Brachial artery reactivity and flow-mediated dilation are reduced by cigarette smoking (63), hypertension (64), hypercholesterolemia (65), and aging (62).

Endothelial Function in Established Vascular Disease

Given these abnormalities in endothelial function in patients with vascular risk factors but without overt vascular disease, it is not surprising that patients with established vascular disease also frequently demonstrate abnormal endothelial function, particularly if risk factors remain uncontrolled. Impaired brachial FMD has been shown to correlate with the extent of CAD and the maximum percentage diameter stenosis in any of the major epicardial coronary arteries (66,67). Similarly, impaired FMD has been reported in an older population with symptomatic peripheral vascular disease (PVD) compared to age-matched controls without apparent PVD (68).

Flow-mediated dilation can also be studied after the administration of exogenous nitroglycerin (NTG); this agent potentiates the vasodilatory response. Several studies have demonstrated that most patients with established vascular disease still potentiate their FMD response. However, when conventional risk factors persist in such patients, the vasodilatory response to NTG is often impaired (69,70). Many conventional risk factors increase the oxidative stress on the endothelium, and the reactive oxygen species that result may lead to more rapid inactivation of endogenous NO and exogenously administered NTG (71).

Vasoresponse after Acute Oxidative Stress: Lipid Challenge in Normal Subjects

Acute ingestion of a high-fat meal results in an acute oxidative stress on human endothelium (72,73); because dietary fat intake is known to be a risk factor for the development of vascular disease, the possibility that acute and chronic dietary habits might lead to endothelial dysfunction and initiate or accelerate atherosclerosis is intriguing. In 1997 Vogel and colleagues reported provocative findings suggesting that acute intake of fat results in acute impairment of endothelial vasoreactivity (74). These investigators studied ten healthy, normocholesterolemic volunteers before and hourly for 6 hours after a single high- (50 g) or low-fat (0 g) meal with brachial artery reactivity. Flow-dependent vasoreactivity decreased from $21 \pm 5\%$ preprandially to $11 \pm 4\%$, $11 \pm 6\%$, and $10 \pm 3\%$ at 2, 3, and 4 hours after the high-fat meal, respectively, whereas a low-fat meal did not produce any changes in FMD (all $ps < 0.05$ compared with the low-fat meal); thus, on average, subjects demonstrated a 50% diminution of brachial artery reactivity. Mean change in postprandial flow-mediated vasoactivity at 2, 3, and 4 hours correlated with change in 2-hour serum triglycerides ($r = -0.51$, $p = 0.02$), suggesting that the fat content of the meal and the effect on postprandial triglyceride levels might be causative. These results suggest that a single high-fat meal transiently impairs endothelial function and might be the link between a high-fat diet and atherogenesis. In a slightly larger study of 20 patients, these investigators replicated these findings and, in addition, generated data to suggest that the detrimental effect of the high-fat meal could be blocked with pretreatment with the antioxidants vitamin C (1 g) and vitamin E (800 IU) (75) (Fig. 1.7). Other investigators have replicated these findings (76–89).

However, other studies have failed to demonstrate acute declines in arterial vasoreactivity following an acute lipid challenge (90–96), with some showing no change, a mixed response, or even vasodilation after fat challenge. Raitakari and colleagues studied 12 normal volunteers before, 3 hours after, and 6 hours after a high-fat meal (61 g) rich in saturated

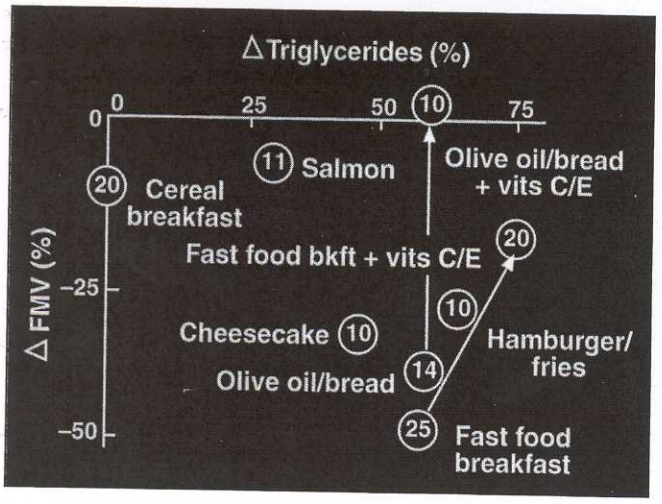

FIG. 1.7. Effect of lipid challenge in normal individuals. Three-hour postprandial changes in triglycerides and flow-mediated vasodilation (FMV) after specific meals. Changes are expressed on the *y* axis as percentage changes versus baseline (prechallenge) FMV. Pretreatment with vitamin E (800 U) and vitamin C (1 gm) restores FMV toward normal values despite fat ingestion. vits, vitamins; bkft, breakfast. (From Vogel R. Brachial artery ultrasound: a noninvasive tool in the assessment of triglyceride-rich lipoproteins. *Clin Cardiol* 1999;22[Suppl II]:II34–II39, with permission.)

fatty acids, 10 of whom were restudied after a similar meal rich in monounsaturated fatty acids (92). Brachial artery basal diameter (assessed by BAR), resting forearm blood flow, and postischemic hyperemia (assessed by plethysmography) increased after high-fat meals, and FMD was unchanged. Thus, in contrast to the previous studies, a high-fat meal was not associated with impaired conduit artery vasoreactivity.

The conflicting results may have several possible explanations. First, there appear to be wide differences among individuals in the FMD response to a high-fat meal, and many other subject-related factors may influence the results, predisposing studies with small numbers of participants vulnerable to Type 1 or Type 2 error. For example, baseline lipoprotein status may affect the results (97). Anderson and colleagues suggested that baseline high-density lipoprotein (HDL) is inversely related to post–high-fat-meal FMD changes (72). Together these observations suggest that baseline lipid status or other metabolic factors among the small numbers of participants in the preceding studies may have accounted for some of the differences. Second, the overall diet of the participants in the weeks before study may affect the response to fat challenge (98), as may consumption of folic acid (79) or a diet rich in fruit and vegetable extracts (89). Third, the biochemical form of the fat may affect the results [trans vs. non-trans (99); the proportion of omega-3-fatty acids (100); whether the fat has been heated to high temperature (101)]. Fourth, there are significant individual differences in the generation of different lipoprotein subfractions after a fat challenge; individuals who generate higher levels of these remnants have been shown to have lower values for preprandial FMD and a larger diminution in postprandial FMD (102). Fifth, because BAR methodology is not yet standardized, methodological differences among protocols are an important confounder (38). Finally, and perhaps most importantly, all of these studies assume that their "normal control" individuals were truly without occult vascular disease.

In summary, acute and chronic dietary composition may play a role in the genesis of endothelial dysfunction, abnormal brachial artery vasoreactivity, and the development of atherosclerosis. Although it is tempting to speculate that this may be a critical factor in the development of disease later in life, the role of dietary-induced endothelial dysfunction, individual genetic variabilities in resistance to such stresses, and the optimal means of assessing it (whether by BAR or some other means) require further study. Ideally, larger studies with long-term follow-up should be performed to prove or disprove this hypothesis.

Vasoresponse after Risk Factor Modification

Hypercholesterolemia

Many studies have reported that risk factor modification and pharmacologic intervention in particular improve endothelial function. In the coronary circulation, serial study of endothelium-mediated dilation (assessed with Ach infusion and either quantitative angiography and/or intracoronary Doppler probes) has been shown to improve after treatment of atherosclerotic risk factors. For example, CAD patients treated for 6 months with cholesterol-lowering 3-hydroxymethylglutamyl coenzyme A reductase (HMG-CoA reductase, or "statin") therapy demonstrate improved or preserved endothelial function compared to patients treated without statins (105). Other trials of lipid lowering (106–108), estrogen replacement (109,110), and ACE inhibition (77) reported serial improvement in flow-mediated dilation. Probuchol, a potent antioxidant, may potentiate this improvement when added to a standard lipid-lowering regimen (111). Using serial positron emission tomography scanning, Gould and colleagues demonstrated significant improvements in myocardial perfusion after only 3 months of therapy (112,113). These observations have led to several large, multicenter clinical trials that are investigating whether intensive risk factor modification rather than revascularization in patients with established CAD can lead to improvements in ischemic episodes compared to conventional treatment (114).

Given that intravascular and necropsy studies demonstrate that substantial coronary atherosclerosis is uniformly present (even if angiographically occult) in patients with clinical PAD, it is somewhat surprising that there are relatively few prospective studies on the effects of HMG-CoA reductase inhibitors on outcomes in patients with peripheral arterial

disease but without overt coronary disease. The recently completed Anglo-Scandanavian Cardiac Outcomes Trial lipid substudy enrolled 261 patients who were diagnosed with PAD but did not have known CAD, and randomized them to atorvastatin 10 mg (without titration to a specific LDL goal) versus placebo (115). In this subgroup, total vascular events were reduced by 20%, in accord with the results of the overall study; however, the 95% confidence intervals were wide (0.45 to 1.42) due to the small number of PVD patients (115). In the absence of additional data, most experts agree that the indications and treatment goals for cholesterol and other risk factors are the same for patients with PAD as for those with CAD. Nevertheless, a recent study documents that only a small fraction of PAD patients are at target levels of cholesterol, blood pressure, and diabetes control (116).

In the absence of large prospective studies, the correlation between coronary and peripheral reactivity in normal individuals and in individuals with risk factors or established vascular disease has led investigators to use peripheral vasoreactivity as a marker for treatment response. A striking finding from many of these studies is the short time period in which a favorable response can be demonstrated. For example, in patients with familial hypercholesterolemia a single LDL apheresis session can improve endothelial function in both the coronary and the peripheral circulation (117). In a small, single-center study of hypercholesterolemic patients, statin therapy improved forearm vasodilator response to acetylcholine infusion in only 4 weeks (118). In patients with acute myocardial infarction or unstable angina, and hypercholesterolemia, statin therapy resulted in a 42% relative improvement in brachial FMD in statin-treated versus placebo, treated patients in 6 weeks (119). Multicenter trials on this issue are nearing completion. The Reversal of Atherosclerosis with Lipitor trial is comparing the ability of a "conventional" (target LDL less than or equal to 100 mg per dL) versus an "aggressive" lipid-lowering strategy (anticipated LDL less than 70 mg per dL) to reduce coronary atheroma volume as measured by IVUS over an 18-month period. A brachial artery reactivity substudy of 220 patients who underwent serial study at 3-month intervals is nearing completion (120).

Angiotensin-Converting Enzyme Inhibition

Endothelial NO production is in part regulated by the renin–angiotensin system, although the details of mechanisms remain to be fully elucidated. In 129 normotensive patients with one- or two-vessel angiographic coronary disease, the Trial on Reversing ENdothelial Dysfunction investigators reported that the angiotensin-converting enzyme inhibitor (ACE-I) quinapril resulted in improved coronary endothelial function compared to placebo as assessed by brachial artery reactivity (121). Anderson and colleagues compared the effects on BAR of quinapril, enalapril, amlodipine, and losartan in 80 patients who had at least one epicardial coronary stenosis of greater than 50% in a crossover design (122). The mean baseline FMD was $7.3 \pm 0.6\%$; quinapril resulted in an absolute increase in FMD of $1.8 \pm 1.0\%$ ($p < 0.02$), whereas the other agents did not result in any significant improvement (122). This observation, along with data from clinical endpoint studies such as the Heart Outcomes Prevention Evaluation (HOPE) Trial (123), has led some investigators to conclude that high tissue-ACE inhibition may be necessary to generate improvements in endothelial function and reduce clinical events (enalapril is a weaker inhibitor of tissue-specific ACE than is quinapril). In the HOPE Trial, 44% of the 9,297 patients had evidence of PAD as determined by an ankle–brachial index (ABI) of 0.9; ramipril reduced cardiovascular events to a similar degree as in patients with normal ABIs. However, the issues of tissue specificity and of whether angiotensin receptor blockers (ARBs) can also produce favorable effects on peripheral vasoreactivity require further study; some smaller studies have suggested that non–tissue-specific ACE and ARBs may improve flow-mediated dilation in diabetics (124–126).

Detrimental Response to Coronary Vasodilators

The ability of available coronary vasodilators to relieve symptoms in either intermittent claudication or critical limb ischemia is disappointing, with the vast majority of studies reporting no benefit. In fact, direct vasodilators theoretically may worsen ischemia in PAD. In coronary disease, these agents exert much of their favorable effect by dilating the systemic vasculature generally, thereby reducing afterload and myocardial oxygen consumption. However, in PAD, vasodilators have no such effect on reducing downstream oxygen consumption. In addition, exercise induces resistance vessels to dilate, whereas resistance vessels in nonexercising tissues remain in a more constricted state. Systemically administered vasodilators might preferentially dilate these territories, creating a "steal" phenomenon. Third, given that peripheral territories (unlike cardiac muscle) receive the majority of blood flow in systole, reduction of systolic pressure may reduce the driving force across peripheral stenoses, particularly long or sequentially diseased segments. Although it is not known whether effective control of hypertension prevents or slows the progression of PAD, attaining current blood pressure targets in hypertensive patients has such a profound effect on reducing overall cardiovascular mortality that these agents should not be withheld due to theoretical concerns of peripheral perfusion, and blood pressure targets should be routinely reached.

Beta-Blockers

Beta-blockers have the potential to perturb the balance of beta- and alpha-receptor activity, which theoretically can result in vasoconstriction. A recent meta-analysis of 11 trials concluded that beta-blockers do not worsen symptoms of

intermittent claudication; because many patients with PAD suffer from known CAD as well, and because these drugs produce a reduction in cardiac death rates in CAD patients, they should not be withheld solely due to the presence of PAD. Nevertheless, clinicians encounter occasional patients whose symptoms are markedly worse when given beta-blockers (127).

Exercise

Exercise is clearly beneficial in patients with intermittent claudication and is discussed in greater detail in Chapter 12. Although the mechanism by which exercise improves symptoms has long been assumed to be the result of increased collateral development, it is also possible that improved peripheral vasoreactivity plays a role. Exercise training improves endothelium-dependent vasodilation in the coronary arteries in CAD patients (128) and in the peripheral circulation in patients with congestive heart failure (129,130). However, other mechanisms, such as favorable alterations in skeletal muscle metabolism, may also be operative (131,132). The relative contribution of each of these mechanisms is unknown.

L-Arginine

The essential amino acid L-arginine is the metabolic precursor to nitric oxide, and its administration can significantly improve vasoreactivity. After L-arginine administration, improvements in flow-mediated dilation can be demonstrated in hypercholesterolemic subjects and in cigarette smokers (104). Interestingly, preliminary studies suggest that L-arginine improves claudication distance in patients with PAD. These and other studies (104,133,134) taken together suggest that in addition to the effects of "fixed" stenoses, endothelial-dependent vasodilation is abnormal in PAD patients and pharmacologic therapies may improve perfusion and symptom status.

Manipulation of Other Endogenous Vasoactive Substances

In addition to nitric oxide, a variety of other vasoactive substances, some derived from the endothelium and others originating in local or distant tissues, influence endothelial function and vasomotor tone. Examples of such substances include prostacyclin, adenosine, prostanoids, serotonin, thrombin, thromboxane, endothelin, and catecholamines. Accordingly, many other pharmacologic agents are in the early stages of development to treat symptomatic peripheral arterial disease, and many such agents are targeted at vasoreactive pathways. Examples of such drugs include novel calcium-channel-blocking agents, angiogenic growth factors, and vasodilator prostaglandins. A serotonin antagonist, naftidrofuryl, has improved claudication symptoms in two studies and is available for clinical use in Europe (135). A multicenter, randomized trial suggests that a cofactor of fatty acid metabolism, proprionyl L-carnitine, can improve intermittent claudication symptoms (136).

Effect of Multiple-Risk-Factor Interventions

Finally, preliminary data suggest that by targeting multiple-risk-factor pathways, one may improve endothelial function further than by treating individual risk factors alone. Nazzaro and colleagues demonstrated that when ACE inhibition was combined with HMG-CoA reductase inhibition in hypercholesterolemic and hypertensive patients without known vascular disease, flow-mediated dilation was improved to a greater degree than with either agent alone (137). This study supports the concept of global risk and the importance of treating multiple risk factors to obtain the largest improvement in endothelial function and, perhaps, in symptom relief. Prospective studies with a larger number of patients are underway.

Atherosclerosis Regression, Disease Stabilization, and Vasoreactivity

Most vascular events are initiated by atheroma rupture or erosion (138), and some researchers have hypothesized that improvement in endothelial function after aggressive risk factor modification may be the mechanism by which rupture/erosion episodes and clinical events are reduced. Because the endothelium also regulates other functions, such as thrombosis, platelet and leukocyte interactions with the vessel wall, and growth factors that regulate smooth muscle cell proliferation and migration, the mechanisms by which an improvement in endothelial function and a reduction in events remain speculative.

Nevertheless, preliminary studies suggest that atheroma volume regression, as assessed either in the coronary circulation with IVUS or in the peripheral circulation with B-mode ultrasound, can occur in humans, and several studies that have coupled morphological and functional assessment indicate that both can improve. In the coronary circulation, lipid lowering is associated with reductions in plaque volume and improvements in lumen area as well as increased IVUS echogenicity (139), which is considered to be a measure of decreased lipid content and lower vulnerability to rupture. Favorable alterations in structure may be associated with improvements in vasoreactivity. Hamasaki et al. studied 101 patients with normal or only mildly diseased (less than 30% angiographic narrowing) left anterior descending coronary artery segments with intravascular ultrasound and assessed endothelial function with intracoronary acetylcholine (140). Patients with a history of total cholesterol greater than 240 mg per dL who had lowered their total cholesterol below this value with medical therapy and those whose initial values were below this level (not on treatment at the time of study) had both larger mean EEM CSA and a greater increase in acetylcholine-induced vasodilation than did patients with

total cholesterol values greater than 240 mg per dL. In this study, mean plaque areas were similar in patients who did and did not have enhanced remodeling and improved endothelial function. Thus, coronary regression may involve favorable remodeling of the EEM CSA along with improved endothelial function, even without measurable differences in plaque volume. The extent to which these favorable, albeit preliminary, changes will be observed in the peripheral circulation is uncertain. In the Antioxidant Supplementation in Atherosclerosis Prevention Study, "aggressive" LDL lowering in patients with familial hypercholesterolemia resulted in regression of carotid intimal–medial thickness as assessed by B-mode ultrasound compared to "less aggressive" LDL lowering (141). Whether individuals with lower starting levels of cholesterol will experience slower disease progression, fewer plaque rupture events, and, perhaps, disease regression is unknown. Large-scale trials of coronary atherosclerosis regression are underway and are discussed in a later section.

Summary: Is Peripheral Arterial Vasoreactivity a New Vascular Risk Factor?

Can peripheral arterial endothelial function, as assessed by brachial artery reactivity, serve as a barometer for the health of the endothelium as a whole? Many studies have documented substantial reductions in major vascular events in both the coronary and the peripheral circulation with adequate control of conventional atherosclerotic risk factors. Endothelial dysfunction precedes the development of overt vascular disease by many years, and abnormal vasoreactivity can frequently be demonstrated in patients without overt clinical atherosclerosis. Risk factor modification (and perhaps treatment with ACE-I or other agents even in normotensive subjects) is associated with improvement in peripheral FMD. Preliminary evidence suggests that this improvement in peripheral FMD is often associated with an improvement in clinical status (111).

Taken together, these observations suggest that assessment of peripheral arterial vasoreactivity with BAR may be useful as a screening tool to detect individuals at higher risk for the development of overt vascular disease. Several studies suggest that peripheral vasoreactivity strongly correlates with clinical outcome. Schachinger and colleagues studied 147 patients at baseline with intracoronary Ach and NTG; during a median follow-up of 7.7 years, patients with abnormal responses had a significantly higher rate of vascular events (cardiovascular death, unstable angina, myocardial infarction, revascularization, or ischemic stroke) (55). Suwaidi and colleagues studied 157 patients with mild angiographic CAD (no lesion with greater than 40% narrowing). During a mean of 28 months follow-up, there were no events in the 32 patients with normal or only mildly abnormal coronary endothelial function, compared to a 14% event rate in the 83 patients with severely impaired coronary response to Ach (percentage change in flow less than 0%) (54). Gokce and colleagues measured BAR in 199 patients prior to elective surgery for peripheral vascular disease; during a mean follow-up of 1.2 years, 18% had a major vascular event (death, myocardial infarction unstable angina, or stroke). Abnormal FMD was an independent predictor of events and conferred a ninefold higher risk (142). Taken together, these data suggest that noninvasive evaluation of peripheral vasoreactivity may become an inexpensive screening tool for identifying individuals at higher risk before the development of overt disease, so that risk factor modification or prophylactic prescription of therapeutic agents could be targeted to these individuals. Nevertheless, most of these studies have been performed in patients with a known disease, multiple uncontrolled risk factors, or a higher-than-average probability of significant occult vascular disease. Two central issues—whether screening for endothelial dysfunction in lower-risk populations will have incremental value to conventional risk factor assessment, and whether intervention (beyond current risk factor goals) will reduce subsequent events or slow disease progression—remain to be resolved. Until adequately designed studies with sufficient numbers of patients prove these relationships, and until the technical and reporting aspects of BAR are further refined, the technique will not be ready for use as a screening or monitoring tool in clinical practice.

Vasoresponse to Injury: Pathophysiologic Mechanisms

Developmental Biology of the Human Vasculature

Although a detailed discussion of arterial embryology is beyond the scope of this chapter, several concepts are vital to a discussion of the arterial response to injury. Human arteries in different beds are heterogeneous, with distinct morphology, physiology, and ability to respond to various pharmacologic agents. During human embryogenesis, all vascular endothelial cells and blood cells are thought to arise from the "blood islands" located at the periphery of the young embryo. However, in different regions of the body, different cell signal mechanisms from surrounding tissues induce considerable heterogeneity in endothelial cell surface receptors (143) and in other cellular functions. For example, the gene that codes for nitric oxide synthase in the coronary arteries has bed-specific regulation (144). Thus, despite their common origin, there is considerable variation in the phenotype of the mature endothelial cells. In contrast to endothelial cells, arterial smooth muscle cells arise from several different locations in the embryo; for example, in the upper part of the body, smooth muscle cells derive from neuroectoderm, whereas in the lower part of the body, a completely different germ layer, the mesoderm, is the source of smooth muscle cells (145). As with endothelial cells, smooth muscle cells demonstrate considerable phenotypic heterogeneity.

The clinical implications of this arterial heterogeneity may profoundly affect the propensity for atherosclerosis to

develop in particular locations and may affect the response of different arterial beds to injury. Atheromatous lesions affect certain key locations preferentially and tend to form at flow dividers and branch points while sparing other characteristic locations (such as the internal thoracic artery) (146–148). The Pathobiologic Determinants of Atherosclerosis in Youth Study collected necropsy specimens from individuals under the age of 35 years who died of noncardiac causes. Fatty streaks and raised arterial lesions initially localize in the dorsal portion of the abdominal aorta, followed by lesion formation in the thoracic aorta (149,150). Right coronary fatty streaks usually follow the development of aortic lesions.

Spontaneous Arterial Injury: Plaque Rupture

The cause of most myocardial infarctions, nonhemorrhagic strokes, and episodes of acute limb ischemia is atherothrombosis. The role of spontaneous plaque rupture as the cause of most acute coronary syndromes is well established (138,151), whereas the frequency with which plaque rupture is responsible for acute events in the peripheral circulation is less well established. There are many reasons why the response to any injury may be different in different arterial beds, including the diverse embryogenesis, the size of the vessels, flow rates, the presence of stenotic regions, and the fact that coronary arteries receive most of their perfusion during diastole, in contrast to peripheral vessels. In addition, peripheral vessels are subject to different hemodynamic stresses. Larger arteries are subjected to larger degrees of circumferential stress, according to the law of Laplace. Accordingly, the large radius of the aorta may make it particularly prone to plaque rupture, and evidence from necropsy and magnetic resonance studies suggests that aortic plaque rupture is a very common occurrence. Even though aortic plaque ruptures are infrequently associated with complete thrombotic occlusion (presumably due to the large residual area even in moderately diseased aortas and the high flow rate), aortic thrombi are a clinically important source of many embolic episodes of acute limb ischemia and stroke. Recent data also suggest that plaque rupture is a common cause of a symptomatic carotid disease. Endarterectomy specimens demonstrate plaque rupture in 74% of symptomatic patients versus only 32% of asymptomatic patients, despite similar degrees of stenosis (152). As with plaque rupture sites in the coronaries, plaque rupture sites in the carotids demonstrate "vulnerable" features, such as thinning of the fibrous cap, lipid-rich or necrotic areas, and infiltration of activated inflammatory cells. Interestingly, the proportion of activated inflammatory cells (as assessed by HLA-DR expression) is higher in ruptured plaque than in specimens from asymptomatic patients (153). Although acute plaque rupture is thought to be an important mechanism for acute syndromes generally in the peripheral circulation, the exact incidence of this phenomenon is unknown (see Chapter 2).

Implications for Long-Term Success of Revascularization of Peripheral Vessels

Therapeutic Arterial Injury (Angioplasty): Outcome in Different Peripheral Territories

Although percutaneous and surgical interventions are discussed in other chapters, the relationships among peripheral arterial morphology and anatomy, vasoreactivity, and pharmacology have a profound impact on strategies for effective percutaneous revascularization. A summary of the literature is complicated by the variety of endpoints utilized; some studies use only angiographic patency rates, whereas others use surrogates of vessel patency or percentage stenosis by duplex ultrasound, ankle–brachial index, or simply the relief of symptoms. Nevertheless, three broad generalizations are warranted by the data. First, the efficacy of percutaneous interventions is better in vessels with good as opposed to poor runoff, that is, when distal vessels are widely patent. Second, the treatment of focal severe stenoses is more successful than the treatment of occlusions (154–156). Third, differences in the acute and long-term success rates of percutaneous interventions in different peripheral arterial territories are striking. For example, iliac artery balloon angioplasty results in a 4- to 5-year patency rate of 60% to 80% (157,158); stent placement improves these numbers to the range of 75% to 95% (159–161). In contrast, the efficacy of balloon angioplasty alone in the femoral and popliteal arteries is less satisfactory. Several registry series have documented 1-, 3-, and 5-year patency rates in the range of 60%, 50%, and 40%, respectively (162,163). Stent placement in the femoral circulation improves these outcomes. Similarly, stent placement in the subclavian and innominate is successful in greater than 85% of cases at 1 year in patients with suitable lesions (164–166).

Unfortunately, with more distal and smaller peripheral vessels, the response to therapeutic injury of angioplasty is far less satisfactory. Balloon angioplasty alone in the peroneal and tibial results in short-term patency rates of less than 50% (155,167–170). Although the results in the infrapopliteal arteries may be skewed by a higher proportion of high-risk patients with unfavorable anatomy and critical limb ischemia, taken together, these studies suggest that vessel size is inversely related to long-term procedural success, especially with balloon angioplasty. Whether the different embryologic origins of these vessels affect the response to therapeutic injury is unknown.

Studies using pre- and postprocedural intravascular ultrasound studies provide insight into the inverse relationship between vessel size and long-term success. Following balloon angioplasty of peripheral vessels, plaque fracture is the most common mechanism of lumen enlargement, followed by atheroma compression/redistribution and, to a lesser degree, vessel "stretch" (171,172). As noted previously, in at least 30% to 40% of advanced femoral arterial stenoses, the EEM area is *less* than that at the reference site (22); in these lesions with "vessel shrinkage," the relative

contribution of stretching may be considerably more important (173). In coronary artery lesions treated with non-stent interventions, Mintz and colleagues used serial intravascular ultrasound in patients with restenosis to document that approximately three-fourths of late lumen loss was due to vessel contraction or shrinkage, whereas only approximately one-fourth was due to neointimal hyperplasia (174,175). Only small serial studies have been done on the peripheral circulation, but these support the notion that vessel constriction after non-stent peripheral interventions is also an important factor in restenosis (176). This observation supports the current widespread use of primary stent deployment because stents minimize or eliminate vessel contraction.

Intravascular Ultrasound Assessment of Peripheral Arterial Stenting

Despite the relatively high long-term patency rates in lesions treated with percutaneous peripheral interventions, a substantial minority of patients experience restenosis or complete occlusion and recurrent symptoms. Whether stent underdeployment, edge dissections, or other suboptimal results (which are frequently angiographically occult, but can be readily diagnosed by IVUS) contribute to the portion of peripheral interventions that fail is unknown. Whether routine or selective intravascular ultrasound utilization could improve clinical outcomes is also unknown. Data suggest that stent underdeployment is common (30% to 40%) and that IVUS can guide more aggressive deployment strategies and result in larger final stent cross-sectional areas (177). Single-center, nonrandomized series suggest that IVUS use in iliac lesions is associated with larger final stent dimensions and higher long-term patency rates (178). Importantly, different peripheral territories may undergo different mechanisms of restenosis after stenting. Using serial intravascular ultrasound, Leertouwer and colleagues demonstrated that renal artery stents suffered substantially less lumen loss from neointimal hyperplasia than did femoropopliteal stents (17% vs. 62%, $p < 0.001$) (178a). In current practice in the United States, IVUS is used in less than 10% of iliac and femoropopliteal interventions, yet the possibility that more liberal utilization would further improve outcomes is untested. Nevertheless, given the inherent limitations of angiography alone, several high-volume peripheral intervention centers report that selective IVUS utilization is invaluable for difficult or challenging cases or when measurements of arterial dimensions are uncertain (179–183).

In the carotid circulation, balloon angioplasty alone was rarely performed due to the potential catastrophic consequences of embolic or thrombotic events. However, carotid stenting in combination with distal protection against atheromatous emboli has recently been shown to be superior to conventional endarterectomy in a multicenter, randomized trial, due to a 50% reduction in acute neurological complications (184). Although many clinicians already consider stenting to be the preferred treatment for most patients with symptomatic carotid disease or critical stenoses, additional studies and appropriate reimbursement will be required before the strategy is universally adopted.

Implications for Restenosis Prevention and Treatment

In large and medium-size peripheral vessels (iliac, innominate, subclavian, femoral, and politeal vessels, carotids, and renals), most interventionalists in the United States treat focal stenoses with stents at the time of initial procedure to minimize the probability of restenosis. This is despite a Dutch study that suggested that provisional rather than routine stent placement is potentially more cost-effective in the iliacs (185), and a small, preliminary study that suggested that brachytherapy after balloon angioplasty of the femoral artery results in excellent 6-month patency and enhanced remodeling compared to use of balloon alone (186). An exception to routine stenting of noncoronary lesions is renal artery fibromuscular dysplasia, which often responds favorably to balloon angioplasty alone (187). In contrast to balloon angioplasty, stent restenosis is almost always due to neointimal hyperplasia [with the occasional exception of stent crush due to trauma in stents that are close to a vulnerable area (188)]. In the coronaries, stents covered with a polymer that contains and secretes one of several cell-cycle inhibitors (all are rapamycin derivatives) in the months after placement have reduced angiographic restenosis rates from the 20% to 40% range to the 0% to 5% range by virtue of their ability to inhibit neointimal hyperplasia, and are in widespread clinical use (189–191). Drug-eluting stents are in development for the periphery, but the larger deployed size of these stents (often greater than 5 to 8 mm) makes polymer adhesion to the struts technologically more challenging than with small (less than 3.5 mm) coronary stents. Furthermore, with clinical restenosis rates already less than 10% in many large peripheral vessels, cost-effectiveness would be unlikely unless the per-unit cost were substantially less than the $3,200 cost per stent in the coronaries. Carotid lesions might become an important exception: Even though restenosis occurs in less than 5% of stented targets, it is often difficult to treat by repeat percutaneous intervention and difficult or impossible to treat surgically (except by carotid bypass) due to the presence of the stent. For this situation, and for restenosis of bare-metal peripheral stents, radiation therapy is in development (192,193).

Vasoreactivity and the Treatment of Peripheral Arterial Disease in the Future

Although revascularization (either surgical or percutaneous) is the predominant strategy for treating severe peripheral arterial disease, the pharmacologic approach is yet to be fully exploited. Compared to the coronary vasculature, the pharmacologic treatment of peripheral disease is in its earliest stages. Angiogenic growth factors to induce next-generation pharmacologic neovascularization agents are in development. In

addition, agents that enhance endothelial function offer another and potentially vital approach to treating these increasingly common diseases. In the coronary circulation, Gould, Lehrman, and others have demonstrated that tissue-level perfusion can be enhanced significantly solely with this approach (112,113,194). It is likely that such agents targeted toward the peripheral circulation will be developed to enhance peripheral perfusion by restoring or enhancing the ability of resistance vessels to regulate flow and deliver blood to downstream tissues, and, perhaps, decrease the incidence of plaque rupture and progression to occlusion. As the prevalence of peripheral arterial disease increases with the aging population, new approaches (such as brachytherapy or drug-eluting stents) will improve the success rates in smaller vessels and total occlusions and will improve long-term success of stenting even further. In the future, revascularization and pharmacologic therapy will be increasingly employed as combined rather than competitive strategies for improving peripheral perfusion, reducing symptoms, and reducing the burden of peripheral arterial disease in these patients.

REFERENCES

1. Tortora GJ, Anagnostakos NP. *Principles of anatomy and physiology,* 6th ed. New York: Harper & Row, 1990:605–653.
2. Harvey W. *Exercitatio anatomica du motu cordis et sanguinis in animalibus,* Leake CD, trans. Springfield, IL: Charles C Thomas, 1928.
3. Donnelly PJ, Wistreich GA. *Laboratory manual for anatomy and physiology.* New York: HarperCollins, 1993:481–515.
4. Schlant RC, Silverman ME, Roberts WC. Anatomy of the heart. In: Hurst JW, Schlant RC, Rackley CE, et al., eds. *The heart: arteries and veins,* 7th ed. New York: McGraw-Hill, 1990:28–35.
5. Ross MH, Reith EJ, Romrell LJ. *Histology.* Baltimore: Williams & Wilkins, 1989:283–305.
6. Moffett DF, Moffett SB, Schauf CL. *Human physiology.* St. Louis: Mosby–Year Book, 1993:299–405.
7. Furchgott RF, Zawadski JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle cell by acetylcholine. *Nature* 1980;228:373–376.
8. Furchgott RF, Vanhoutte PM. Endothelium derived relaxing and contracting factors. *FASEB J* 1989;3:2007–2018.
9. Taylor SG, Weston AH. Endothelium derived hyperpolarizing factor: a new endogenous inhibitor from vascular endothelium. *Trends Pharmacol Sci* 1988;9:272–274.
10. Furchgott RF. Introduction to EDRF research. *J Cardiovasc Pharmacol* 1993;22[Suppl 7]:S1–S2.
11. Stato T, Arai K, Ishiharajima S, et al. Role of glycosaminoglycan and fibronectin in endothelial cell growth. *Exp Mol Pathol* 1987;47:202–210.
12. Vlodavsky I, Fielding PE, Johnson LK, et al. Inhibition of LDL uptake in endothelium correlates with a restricted surface receptor redistribution. *J Cell Physiol* 1979;100:481–495.
13. Gryglewski RJ, Botting RM, Vane JR. Mediators produced by the endothelial cell. *Hypertension* 1988;12:530–548.
14. Schorer AE, Moldow CF. Production of tissue factor. In: Ryan US, ed. *Endothelial cells.* Boca Raton, FL: CRC Press, 1988:85.
15. Rapoport RM, Draznin MB, Murad F. Endothelium dependent relaxation in rat aorta may be mediated through cyclic GMP dependent protein phosphorylation. *Nature* 1983;306:174–176.
16. Langille BL, O'Donnell F. Reductions in arterial diameter produced by chronic decreases in blood flow are endothelium dependent. *Science* 1986;231:405–407.
17. Glagov S, Weisenberg E, Zarins C, et al. Compensatory enlargement of human atherosclerotic coronary arteries. *N Engl J Med* 1987;316:1371–1375.
18. Schoenhagen P, Nissen SE, Tuzcu EM. Coronary arterial remodeling: from bench to bedside. *Curr Atheroscler Rep* 2003;5:150–154.
19. Schoenhagen P, Ziada KM, Vince DG, et al. Arterial remodeling and coronary artery disease: the concept of "dilated" versus "obstructive" coronary atherosclerosis. *J Am Coll Cardiol* 2001;38:297–306.
20. Schoenhagen P, Ziada KM, Kapadia SR, et al. Extent and direction of arterial remodeling in stable versus unstable coronary syndromes: an intravascular ultrasound study. *Circulation* 2000;101:598–603.
21. Hagenaars T, Gussenhoven EJ, Athanassopoulos P, et al. Intravascular ultrasound evidence for stabilization of compensatory enlargement of the femoropopliteal segment after endograft placement. *J Endovasc Ther* 2001;8:308–314.
22. Pasterkamp G, Wensing PJ, Post MJ, et al. Paradoxical arterial wall shrinkage may contribute to luminal narrowing of human atherosclerotic femoral arteries. *Circulation* 1995;91:1444–1449.
23. Mintz GS, Kent KM, Pichard AD, et al. Contribution of inadequate arterial remodeling to the development of focal coronary artery stenoses. An intravascular ultrasound study. *Circulation* 1997;95:1791–1798.
24. Hagenaars T, Gussenhoven EJ, Poldermans D, et al. Rationale and design for the SARIS trial; effect of statin on atherosclerosis and vascular remodeling assessed with intravascular sonography. *Cardiovasc Drugs Ther* 2001;15:339–343.
25. Olesen SP, Clapham DE, Davies PF. Haemodynamic shear stress activates a K+ current in vascular endothelial cells. *Nature* 1988;331:168–170.
26. Cooke JP, Rossitch Jr E, Andon NA, et al. Flow activates an endothelial potassium channel to release an endogenous nitrovasodilator. *J Clin Invest* 1991;88:1663–1671.
27. Miura H, Wachtel RE, Liu Y, et al. Flow-induced dilation of human coronary arterioles: important role of Ca(2+)-activated K(+) channels. *Circulation* 2001;103:1992–1998.
28. Pohl U, Holtz J, Busse R, et al. Crucial role of endothelium in the vasodilator response to increased flow *in vivo*. *Hypertension* 1986;8:37–44.
29. Joannides R, Haefeli WE, Linder L, et al. Nitric oxide is responsible for flow-dependent dilatation of human peripheral conduit arteries *in vivo*. *Circulation* 1995;91:1314–1319.
30. Sun D, Huang A, Smith CJ, et al. Enhanced release of prostaglandins contributes to flow-induced arteriolar dilation in eNOS knockout mice. *Circ Res* 1999;85:288–293.
31. Zir L, Miller S, Dinsmore R, et al. Interobserver variability in coronary angiography. *Circulation* 1976;53:627–632.
32. Arnett E, Isner J, Redwood C, et al. Coronary artery narrowing in coronary heart disease: comparison of cineangiographic and necropsy findings. *Ann Intern Med* 1979;91:350–356.
33. Isner J, Kishel J, Kent K. Accuracy of angiographic determination of left main coronary arterial narrowing. *Circulation* 1981;63:1056–1061.
34. Isner JM, Donaldsen RF. Coronary angiographic and morphologic correlaton. In: Waller BF, ed. *Cardiac morphology.* Philadelphia: Saunders, 1984:571–592.
35. Werns SW, Walton JA, Hsia HH, et al. Evidence of endothelial dysfunction in angiographically normal coronary arteries of patients with coronary artery disease. *Circulation* 1989;79:287–291.
36. Oemar BS, Tschudi MR, Godoy N, et al. Reduced endothelial nitric oxide synthase expression and production in human atherosclerosis. *Circulation* 1998;97:2494–2498.
37. Uehata A, Lieberman EH, Gerhard MD, et al. Noninvasive assessment of endothelium-dependent flow-mediated dilation of the brachial artery. *Vasc Med* 1997;2:87–92.
38. Vogel RA, Corretti MC, Plotnick GD. A comparison of brachial artery flow-mediated vasodilation using upper and lower arm arterial occlusion in subjects with and without coronary risk factors. *Clin Cardiol* 2000;23:571–575.
39. Corretti MC, Plotnick GD, Vogel RA. Technical aspects of evaluating brachial artery vasodilatation using high-frequency ultrasound. *Am J Physiol* 1995;268:H1397–H1404.
40. Lieberman EH, Gerhard MD, Uehata A, et al. Flow-induced vasodilation of the human brachial artery is impaired in patients less than 40 years of age with coronary artery disease. *Am J Cardiol* 1996;78:1210–1214.
41. Joannides R, Richard V, Haefeli WE, et al. Role of nitric oxide in the regulation of the mechanical properties of peripheral conduit arteries in humans. *Hypertension* 1997;30:1465–1470.

42. Celermajer DS, Sorensen KE, Gooch VM, et al. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. *Lancet* 1992;340:1111–1115.
43. Corretti MC, Anderson TJ, Benjamin EJ, et al. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. *J Am Coll Cardiol* 2002;39:257–265.
44. Leeson P, Thorne S, Donald A, et al. Non-invasive measurement of endothelial function: effect on brachial artery dilatation of graded endothelial dependent and independent stimuli. *Heart* 1997;78:22–27.
45. Stadler RW, Ibrahim SF, Lees RS. Measurement of the time course of peripheral vasoactivity: results in cigarette smokers. *Atherosclerosis* 1998;138:197–205.
46. Hashimoto M, Akishita M, Eto M, et al. Modulation of endothelium-dependent flow-mediated dilatation of the brachial artery by sex and menstrual cycle. *Circulation* 1995;92:3431–3435.
47. Hardie KL, Kinlay S, Hardy DB, et al. Reproducibility of brachial ultrasonography and flow-mediated dilatation (FMD) for assessing endothelial function. *Aust N Z J Med* 1997;27:649–652.
48. Ross R. Atherosclerosis: current understanding of mechanisms and future strategies in therapy. *Transplant Proc* 1993;25:2041–2043.
49. Corretti MC, Plotnick GD, Vogel RA. The effects of age and gender on brachial artery endothelium-dependent vasoactivity are stimulus-dependent. *Clin Cardiol* 1995;18:471–476.
50. Joseph A, Ackerman D, Talley JD, et al. Manifestations of coronary atherosclerosis in young trauma victims—an autopsy study. *J Am Coll Cardiol* 1993;22:459–467.
51. Stary HC. Evolution and progression of atherosclerotic lesions in coronary arteries of children and young adults. *Arteriosclerosis* 1989;9[1 Suppl]:I19–I32.
52. Berenson GS, Srinivasan SR, Bao W, et al. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. *N Engl J Med* 1998;338:1650–1656.
53. Tuzcu EM, Hobbs RE, Rincon G, et al. Occult and frequent transmission of atherosclerotic coronary disease with cardiac transplantation. Insights from intravascular ultrasound. *Circulation* 1995;91:1706–1713.
54. Suwaidi JA, Hamasaki S, Higano ST, et al. Long-term follow-up of patients with mild coronary artery disease and endothelial dysfunction. *Circulation* 2000;101:948–954.
55. Schachinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. *Circulation* 2000;101:1899–1906.
56. Schroeder S, Enderle MD, Ossen R, et al. Noninvasive determination of endothelium-mediated vasodilation as a screening test for coronary artery disease: pilot study to assess the predictive value in comparison with angina pectoris, exercise electrocardiography, and myocardial perfusion imaging. *Am Heart J* 1999;138:731–739.
57. Vogel RA, Corretti MC. Estrogens, progestins, and heart disease: can endothelial function divine the benefit? *Circulation* 1998;97:1223–1226.
58. Celermajer DS, Sorensen KE, Bull C, et al. Endothelium-dependent dilation in the systemic arteries of asymptomatic subjects relates to coronary risk factors and their interaction. *J Am Coll Cardiol* 1994;24:1468–1474.
59. Perticone F, Ceravolo R, Pujia A, et al. Prognostic significance of endothelial dysfunction in hypertensive patients. *Circulation* 2001;104:191–196.
60. Gardillo C, Kilcoyne CM, Quyyumi AA, et al. Selective defect in nitric oxide synthesis may explain the impaired endothelium-dependent vasodilation in patients with essential hypertension. *Circulation* 1998;97:851–856.
61. Arcaro G, Zenere BM, Travia D, et al. Non-invasive detection of early endothelial dysfunction in hypercholesterolaemic subjects. *Atherosclerosis* 1995;114:247–254.
62. Gerhard M, Roddy MA, Creager SJ, et al. Aging progressively impairs endothelium-dependent vasodilation in forearm resistance vessels of humans. *Hypertension* 1996;27:849–853.
63. Celermajer DS, Sorensen KE, Georgakopoulos D, et al. Cigarette smoking is associated with dose-related and potentially reversible impairment of endothelium-dependent dilation in healthy young adults. *Circulation* 1993;88:2149–2155.
64. Laurent S, Lacolley P, Brunel P, et al. Flow-dependent vasodilation of brachial artery in essential hypertension. *Am J Physiol* 1990;258:H1004–1011.
65. Steinberg HO, Bayazeed B, Hook G, et al. Endothelial dysfunction is associated with cholesterol levels in the high normal range in humans. *Circulation* 1997;96:3287–3293.
66. Corretti MC, Plotnick GD, Vogel RA. Correlation of cold pressor and flow-mediated brachial artery diameter responses with the presence of coronary artery disease. *Am J Cardiol* 1995;75:783–787.
67. Neunteufl T, Katzenschlager R, Hassan A, et al. Systemic endothelial dysfunction is related to the extent and severity of coronary artery disease. *Atherosclerosis* 1997;129:111–118.
68. Yataco AR, Corretti MC, Gardner AW, et al. Endothelial reactivity and cardiac risk factors in older patients with peripheral arterial disease. *Am J Cardiol* 1999;83:754–758.
69. Adams MR, Robinson J, McCredie R, et al. Smooth muscle dysfunction occurs independently of impaired endothelium-dependent dilation in adults at risk of atherosclerosis. *J Am Coll Cardiol* 1998;32:123–127.
70. Bhagat K, Hingorani A, Vallance P. Flow associated or flow mediated dilatation? More than just semantics. *Heart* 1997;78:7–8.
71. Ohara Y, Peterson TE, Harrison DG. Hypercholesterolemia increases endothelial superoxide anion production. *J Clin Invest* 1993;91:2546–2551.
72. Anderson RA, Evans ML, Ellis GR, et al. The relationships between post-prandial lipaemia, endothelial function and oxidative stress in healthy individuals and patients with type 2 diabetes. *Atherosclerosis* 2001;154:475–483.
73. Nappo F, Esposito K, Cioffi M, et al. Postprandial endothelial activation in healthy subjects and in type 2 diabetic patients: role of fat and carbohydrate meals. *J Am Coll Cardiol* 2002;39:1145–1150.
74. Vogel RA, Corretti MC, Plotnick GD. Effect of a single high-fat meal on endothelial function in healthy subjects. *Am J Cardiol* 1997;79:350–354.
75. Plotnick GD, Corretti MC, Vogel RA. Effect of antioxidant vitamins on the transient impairment of endothelium-dependent brachial artery vasoactivity following a single high-fat meal. *JAMA* 1997;278:1682–1686.
76. Lundman P, Eriksson M, Schenck-Gustafsson K, et al. Transient triglyceridemia decreases vascular reactivity in young, healthy men without risk factors for coronary heart disease. *Circulation* 1997;96:3266–3268.
77. Wilmink HW, Banga JD, Hijmering M, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II type 1 receptor antagonism on postprandial endothelial function. *J Am Coll Cardiol* 1999;34:140–145.
78. Ong PJ, Dean TS, Hayward CS, et al. Effect of fat and carbohydrate consumption on endothelial function. *Lancet* 1999;354:2134.
79. Wilmink HW, Stroes ES, Erkelens WD, et al. Influence of folic acid on postprandial endothelial dysfunction. *Arterioscler Thromb Vasc Biol* 2000;20:185–188.
80. Cuevas AM, Guasch V, Castillo O, et al. A high-fat diet induces and red wine counteracts endothelial dysfunction in human volunteers. *Lipids* 2000;35:143–148.
81. Marchesi S, Lupattelli G, Schillaci G, et al. Impaired flow-mediated vasoactivity during post-prandial phase in young healthy men. *Atherosclerosis* 2000;153:397–402.
82. Schinkovitz A, Dittrich P, Wascher TC. Effects of a high-fat meal on resistance vessel reactivity and on indicators of oxidative stress in healthy volunteers. *Clin Physiol* 2001;21:404–410.
83. Gaenzer H, Sturm W, Neumayr G, et al. Pronounced postprandial lipemia impairs endothelium-dependent dilation of the brachial artery in men. *Cardiovasc Res* 2001;52:509–516.
84. 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.
85. Zhao SP, Liu L, Gao M, et al. Impairment of endothelial function after a high-fat meal in patients with coronary artery disease. *Coron Artery Dis* 2001;12:561–565.
86. Hozumi T, Eisenberg M, Sugioka K, et al. Change in coronary flow reserve on transthoracic Doppler echocardiography after a single high-fat meal in young healthy men. *Ann Intern Med* 2002;136:523–528.

87. Ling L, Zhao SP, Gao M, et al. Vitamin C preserves endothelial function in patients with coronary heart disease after a high-fat meal. *Clin Cardiol* 2002;25:219–224.
88. Bae JH, Schwemmer M, Lee IK, et al. Postprandial hypertriglyceridemia-induced endothelial dysfunction in healthy subjects is independent of lipid oxidation. *Int J Cardiol* 2003;87:259–267.
89. Plotnick GD, Corretti MC, Vogel RA, et al. Effect of supplemental phytonutrients on impairment of the flow-mediated brachial artery vasoactivity after a single high-fat meal. *J Am Coll Cardiol* 2003;41:1744–1749.
90. Djousse L, Ellison RC, McLennan CE, et al. Acute effects of a high-fat meal with and without red wine on endothelial function in healthy subjects. *Am J Cardiol* 1999;84:660–664.
91. Gudmundsson GS, Sinkey CA, Chenard CA, et al. Resistance vessel endothelial function in healthy humans during transient postprandial hypertriglyceridemia. *Am J Cardiol* 2000;85:381–385.
92. Raitakari OT, Lai N, Griffiths K, et al. Enhanced peripheral vasodilation in humans after a fatty meal. *J Am Coll Cardiol* 2000;36:417–422.
93. Gokce N, Duffy SJ, Hunter LM, et al. Acute hypertriglyceridemia is associated with peripheral vasodilation and increased basal flow in healthy young adults. *Am J Cardiol* 2001;88:153–159.
94. Katz DL, Nawaz H, Boukhalil J, et al. Acute effects of oats and vitamin E on endothelial responses to ingested fat. *Am J Prev Med* 2001;20:124–129.
95. Sarabi M, Fugmann A, Karlstrom B, et al. An ordinary mixed meal transiently impairs endothelium-dependent vasodilation in healthy subjects. *Acta Physiol Scand* 2001;172:107–113.
96. Edwards C, Stewart RA, Ramanathan K, et al. Increased myocardial ischemia after food is not explained by endothelial dysfunction. *Am Heart J* 2002;144(5):E8 2002 Nov:789.
97. Vogel RA, Corretti MC, Plotnick GD. Changes in flow-mediated brachial artery vasoactivity with lowering of desirable cholesterol levels in healthy middle-aged men. *Am J Cardiol* 1996;77:37–40.
98. Fuentes F, Lopez-Miranda J, Sanchez E, et al. Mediterranean and low-fat diets improve endothelial function in hypercholesterolemic men. *Ann Intern Med* 2001;134:1115–1119.
99. de Roos NM, Bots ML, Katan MB. Replacement of dietary saturated fatty acids by trans fatty acids lowers serum HDL cholesterol and impairs endothelial function in healthy men and women. *Arterioscler Thromb Vasc Biol* 2001;21:1233–1237.
100. 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.
101. Williams MJ, Sutherland WH, McCormick MP, et al. Impaired endothelial function following a meal rich in used cooking fat. *J Am Coll Cardiol* 1999;33:1050–1055.
102. Funada J, Sekiya M, Hamada M, et al. Postprandial elevation of remnant lipoprotein leads to endothelial dysfunction. *Circ J* 2002;66:127–132.
103. Levine GN, Frei B, Koulouris SN, et al. Ascorbic acid reverses endothelial vasomotor dysfunction in patients with coronary artery disease. *Circulation* 1996;93:1107–1113.
104. Thorne S, Mullen MJ, Clarkson P, et al. Early endothelial dysfunction in adults at risk from atherosclerosis: different responses to L-arginine. *J Am Coll Cardiol* 1998;32:110–116.
105. Treasure CB, Klein JL, Weintraub WS, et al. Beneficial effects of cholesterol-lowering therapy on the coronary endothelium in patients with coronary artery disease. *N Engl J Med* 1995;332:481–487.
106. Koh KK, Cardillo C, Bui MN, et al. Vascular effects of estrogen and cholesterol-lowering therapies in hypercholesterolemic postmenopausal women. *Circulation* 1999;99:354–360.
107. Megnien JL, Simon A, Andriani A, et al. Cholesterol lowering therapy inhibits the low-flow mediated vasoconstriction of the brachial artery in hypercholesterolaemic subjects. *Br J Clin Pharmacol* 1996;42:187–193.
108. Cohen JD, Drury JH, Ostdiek J, et al. Benefits of lipid lowering on vascular reactivity in patients with coronary artery disease and average cholesterol levels: a mechanism for reducing clinical events? *Am Heart J* 2000;139:734–738.
109. Lieberman EH, Gerhard MD, Uehata A, et al. Estrogen improves endothelium-dependent, flow-mediated vasodilation in postmenopausal women. *Ann Intern Med* 1994;121:936–941.
110. Gerhard M, Walsh BW, Tawakol A, et al. Estradiol therapy combined with progesterone and endothelium-dependent vasodilation in postmenopausal women. *Circulation* 1998;98:1158–1163.
111. Anderson TJ, Meredith IT, Yeung AC, et al. The effect of cholesterol-lowering and antioxidant therapy on endothelium-dependent coronary vasomotion. *N Engl J Med* 1995;332:488–493.
112. Gould KL, Martucci JP, Goldberg DI, et al. Short-term cholesterol lowering decreases size and severity of perfusion abnormalities by positron emission tomography after dipyridamole in patients with coronary artery disease. A potential noninvasive marker of healing coronary endothelium. *Circulation* 1994;89:1530–1538.
113. Gould KL, Ornish D, Scherwitz L, et al. Changes in myocardial perfusion abnormalities by positron emission tomography after long-term, intense risk factor modification. *JAMA* 1995;274:894–901.
114. Chiquette E, Chilton R. Aggressive medical management of coronary artery disease versus mechanical revascularization. *Curr Atheroscler Rep* 2003;5:118–123.
115. Sever PS, Dahlof B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003;361:1149–1158.
116. Mukherjee D, Lingam P, Chetcuti S, et al. Missed opportunities to treat atherosclerosis in patients undergoing peripheral vascular interventions: insights from the University of Michigan Peripheral Vascular Disease Quality Improvement Initiative (PVD-QI2). *Circulation* 2002;106:1909–1912.
117. Tamai O, Matsuoka H, Itabe H, et al. Single LDL apheresis improves endothelium-dependent vasodilatation in hypercholesterolemic humans. *Circulation* 1997;95:76–82.
118. O'Driscoll G, Green D, Taylor RR. Simvastatin, an HMG–coenzyme A reductase inhibitor, improves endothelial function within 1 month. *Circulation* 1997;95:1126–1131.
119. Dupuis J, Tardif JC, Cernacek P, et al. Cholesterol reduction rapidly improves endothelial function after acute coronary syndromes. The RECIFE (Reduction of Cholesterol in Ischemia and Function of the Endothelium) Trial. *Circulation* 1999;99:3227–3233.
120. Nissen SE. Rationale for a postintervention continuum of care: insights from intravascular ultrasound. *Am J Cardiol* 2000;86:12H–17H.
121. Mancini GB, Henry GC, Macaya C, et al. Angiotensin-converting enzyme inhibition with quinapril improves endothelial vasomotor dysfunction in patients with coronary artery disease. The TREND (Trial on Reversing ENdothelial Dysfunction) Study. *Circulation* 1996;94:258–265.
122. Anderson TJ, Elstein E, Haber H, et al. Comparative study of ACE-inhibition, angiotensin II antagonism, and calcium channel blockade on flow-mediated vasodilation in patients with coronary disease (BANFF study). *J Am Coll Cardiol* 2000;35:60–66.
123. 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 Engl J Med* 2000;342:145–153.
124. Mullen MJ, Clarkson P, Donald AE, et al. Effect of enalapril on endothelial function in young insulin-dependent diabetic patients: a randomized, double-blind study. *J Am Coll Cardiol* 1998;31:1330–1335.
125. O'Driscoll G, Green D, Maiorana A, et al. Improvement in endothelial function by angiotensin-converting enzyme inhibition in non-insulin-dependent diabetes mellitus. *J Am Coll Cardiol* 1999;33:1506–1511.
126. Cheetham C, Collis J, O'Driscoll G, et al. Losartan, an angiotensin type 1 receptor antagonist, improves endothelial function in non-insulin-dependent diabetes. *J Am Coll Cardiol* 2000;36:1461–1466.
127. Tzemos N, Lim PO, MacDonald TM. Nebivolol reverses endothelial dysfunction in essential hypertension: a randomized, double-blind, crossover study. *Circulation* 2001;104:511–514.
128. Hambrecht R, Wolf A, Gielen S, et al. Effect of exercise on coronary endothelial function in patients with coronary artery disease. *N Engl J Med* 2000;342:454–460.
129. Hambrecht R, Fiehn E, Weigl C, et al. Regular physical exercise corrects endothelial dysfunction and improves exercise capacity in patients with chronic heart failure. *Circulation* 1998;98:2709–2715.

130. Hornig B, Maier V, Drexler H. Physical training improves endothelial function in patients with chronic heart failure. *Circulation* 1996;93:210–214.
131. Hiatt WR, Regensteiner JG, Hargarten ME, et al. Benefit of exercise conditioning for patients with peripheral arterial disease. *Circulation* 1990;81:602–609.
132. Hiatt WR, Regensteiner JG, Wolfel EE, et al. Effect of exercise training on skeletal muscle histology and metabolism in peripheral arterial disease. *J Appl Physiol* 1996;81:780–788.
133. Schellong SM, Boger RH, Burchert W, et al. Dose-related effect of intravenous L-arginine on muscular blood flow of the calf in patients with peripheral vascular disease: a $H_2{}^{15}O$ positron emission tomography study. *Clin Sci* (Lond) 1997;93:159–165.
134. Boger RH, Bode-Boger SM, Thiele W, et al. Restoring vascular nitric oxide formation by L-arginine improves the symptoms of intermittent claudication in patients with peripheral arterial occlusive disease. *J Am Coll Cardiol* 1998;32:1336–44.
135. Barradell LB, Brogden RN. Oral naftidrofuryl. A review of its pharmacology and therapeutic use in the management of peripheral occlusive arterial disease. *Drugs Aging* 1996;8:299–322.
136. Brevetti G, Diehm C, Lambert D. European multicenter study on propionyl-L-carnitine in intermittent claudication. *J Am Coll Cardiol* 1999;34:1618–1624.
137. Nazzaro P, Manzari M, Merlo M, et al. Distinct and combined vascular effects of ACE blockade and HMG–CoA reductase inhibition in hypertensive subjects. *Hypertension* 1999;33:719–725.
138. Virmani R, Burke AP, Farb A, et al. Pathology of the unstable plaque. *Prog Cardiovasc Dis* 2002;44:349–356.
139. Schartl M, Bocksch W, Koschyk DH, et al. Use of intravascular ultrasound to compare effects of different strategies of lipid-lowering therapy on plaque volume and composition in patients with coronary artery disease. *Circulation* 2001;104:387–392.
140. Hamasaki S, Higano ST, Suwaidi JA, et al. Cholesterol-lowering treatment is associated with improvement in coronary vascular remodeling and endothelial function in patients with normal or mildly diseased coronary arteries. *Arterioscler Thromb Vasc Biol* 2000;20:737–743.
141. Smilde TJ, van Wissen S, Wollersheim H, et al. Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolaemia (ASAP): a prospective, randomised, double-blind trial. *Lancet* 2001;357:577–581.
142. Gokce N, Keaney Jr JF, Hunter LM, et al. Predictive value of noninvasively determined endothelial dysfunction for long-term cardiovascular events in patients with peripheral vascular disease. *J Am Coll Cardiol* 2003;41:1769–1775.
143. Adams RH, Wilkinson GA, Weiss C, et al. Roles of ephrinB ligands and EphB receptors in cardiovascular development: demarcation of arterial/venous domains, vascular morphogenesis, and sprouting angiogenesis. *Genes Dev* 1999;13:295–306.
144. Guillot PV, Guan J, Liu L, et al. A vascular bed-specific pathway. *J Clin Invest* 1999;103:799–805.
145. Bergwerff M, Verberne ME, DeRuiter MC, et al. Neural crest cell contribution to the developing circulatory system: implications for vascular morphology? *Circ Res* 1998;82:221–231.
146. Ikari Y, McManus BM, Kenyon J, et al. Neonatal intima formation in the human coronary artery. *Arterioscler Thromb Vasc Biol* 1999;19:2036–2040.
147. Weninger WJ, Muller GB, Reiter C, et al. Intimal hyperplasia of the infant parasellar carotid artery: a potential developmental factor in atherosclerosis and SIDS. *Circ Res* 1999;85:970–975.
148. Schwartz SM. The intima: a new soil. *Circ Res* 1999;85:877–879.
149. Rainwater DL, McMahan CA, Malcom GT, et al. Lipid and apolipoprotein predictors of atherosclerosis in youth: apolipoprotein concentrations do not materially improve prediction of arterial lesions in PDAY subjects. The PDAY Research Group. *Arterioscler Thromb Vasc Biol* 1999;19:753–761.
150. Strong JP, Malcom GT, Oalmann MC, et al. The PDAY Study: natural history, risk factors, and pathobiology. Pathobiological Determinants of Atherosclerosis in Youth. *Ann NY Acad Sci* 1997;811:226–235; discussion 235–237.
151. Virmani R, Burke AP, Kolodgie FD, et al. Vulnerable plaque: the pathology of unstable coronary lesions. *J Interv Cardiol* 2002;15:439–446.
152. Carr S, Farb A, Pearce WH, et al. Atherosclerotic plaque rupture in symptomatic carotid artery stenosis. *J Vasc Surg* 1996;23:755–765; discussion 765–756.
153. Carr SC, Farb A, Pearce WH, et al. Activated inflammatory cells are associated with plaque rupture in carotid artery stenosis. *Surgery* 1997;122:757–763; discussion 763–764.
154. Gupta AK, Ravimandalam K, Rao VR, et al. Total occlusion of iliac arteries: results of balloon angioplasty. *Cardiovasc Intervent Radiol* 1993;16:165–177.
155. Pentecost MJ, Criqui MH, Dorros G, et al. Guidelines for peripheral percutaneous transluminal angioplasty of the abdominal aorta and lower extremity vessels. A statement for health professionals from a special writing group of the Councils on Cardiovascular Radiology, Arteriosclerosis, Cardio-Thoracic and Vascular Surgery, Clinical Cardiology, and Epidemiology and Prevention, the American Heart Association. *Circulation* 1994;89:511–531.
156. Motarjeme A, Gordon GI, Bodenhagen K. Thrombolysis and angioplasty of chronic iliac artery occlusions. *J Vasc Interv Radiol* 1995; 6[6 Pt 2 Supp]:66S–72S.
157. Johnston KW. Iliac arteries: reanalysis of results of balloon angioplasty. *Radiology* 1993;186:207–212.
158. Tegtmeyer CJ, Hartwell GD, Selby JB, et al. Results and complications of angioplasty in aortoiliac disease. *Circulation* 1991; 83[2 Suppl]:I53–I60.
159. Henry M, Amor M, Ethevenot G, et al. Palmaz stent placement in iliac and femoropopliteal arteries: primary and secondary patency in 310 patients with 2–4-year follow-up. *Radiology* 1995;197:167–174.
160. Sullivan TM, Childs MB, Bacharach JM, et al. Percutaneous transluminal angioplasty and primary stenting of the iliac arteries in 288 patients. *J Vasc Surg* 1997;25:829–838; discussion 838–839.
161. 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.
162. Matsi PJ, Manninen HI. Complications of lower-limb percutaneous transluminal angioplasty: a prospective analysis of 410 procedures on 295 consecutive patients. *Cardiovasc Intervent Radiol* 1998;21:361–366.
163. Hunink MG, Donaldson MC, Meyerovitz MF, et al. Risks and benefits of femoropopliteal percutaneous balloon angioplasty. *J Vasc Surg* 1993;17:183–192; discussion 192–194.
164. Sullivan TM, Gray BH, Bacharach JM, et al. Angioplasty and primary stenting of the subclavian, innominate, and common carotid arteries in 83 patients. *J Vasc Surg* 1998;28:1059–1065.
165. Mathias KD, Luth I, Haarmann P. Percutaneous transluminal angioplasty of proximal subclavian artery occlusions. *Cardiovasc Intervent Radiol* 1993;16:214–218.
166. Millaire A, Trinca M, Marache P, et al. Subclavian angioplasty: immediate and late results in 50 patients. *Cathet Cardiovasc Diagn* 1993;29:8–17.
167. Bakal CW, Sprayregen S, Scheinbaum K, et al. Percutaneous transluminal angioplasty of the infrapopliteal arteries: results in 53 patients. *AJR Am J Roentgenol* 1990;154:171–174.
168. Bakal CW, Cynamon J, Sprayregen S. Infrapopliteal percutaneous transluminal angioplasty: what we know. *Radiology* 1996;200:36–43.
169. Matsi PJ, Manninen HI, Suhonen MT, et al. Chronic critical lower-limb ischemia: prospective trial of angioplasty with 1–36 months follow-up. *Radiology* 1993;188:381–387.
170. Dorros G, Jaff MR, Murphy KJ, et al. The acute outcome of tibioperoneal vessel angioplasty in 417 cases with claudication and critical limb ischemia. *Cathet Cardiovasc Diagn* 1998;45:251–256.
171. The SH, Gussenhoven EJ, Zhong Y, et al. Effect of balloon angioplasty on femoral artery evaluated with intravascular ultrasound imaging. *Circulation* 1992;86:483–493.
172. Losordo DW, Rosenfield K, Pieczek A, et al. How does angioplasty work? Serial analysis of human iliac arteries using intravascular ultrasound. *Circulation* 1992;86:1845–1858.
173. Pasterkamp G, Borst C, Gussenhoven EJ, et al. Remodeling of *de novo* atherosclerotic lesions in femoral arteries: impact on mechanism of balloon angioplasty. *J Am Coll Cardiol* 1995;26:422–428.
174. de Vrey EA, Mintz GS, von Birgelen C, et al. Serial volumetric (three-dimensional) intravascular ultrasound analysis of restenosis after directional coronary atherectomy. *Journal of the American College of Cardiology* 1998;32:1874–1880.

175. Mintz GS, Kimura T, Nobuyoshi M, et al. Intravascular ultrasound assessment of the relation between early and late changes in arterial area and neointimal hyperplasia after percutaneous transluminal coronary angioplasty and directional coronary atherectomy. *American Journal of Cardiology* 1999;83:1518–1523.
176. van Lankeren W, Gussenhoven EJ, Honkoop J, et al. Plaque area increase and vascular remodeling contribute to lumen area change after percutaneous transluminal angioplasty of the femoropopliteal artery: an intravascular ultrasound study. *J Vasc Surg* 1999;29:430–441.
177. Arko F, McCollough R, Manning L, et al. Use of intravascular ultrasound in the endovascular management of atherosclerotic aortoiliac occlusive disease. *Am J Surg* 1996;172:546–549; discussion 549–550.
178. Buckley CJ, Arko FR, Lee S, et al. Intravascular ultrasound scanning improves long-term patency of iliac lesions treated with balloon angioplasty and primary stenting. *J Vasc Surg* 2002;35:316–323.
178a. Leertouwer TC, Gussenhoven EJ, van Lankeren W, et al. Response of renal and femoropopliteal arteries to Palmaz stent implantation assessed with intravascular ultrasound. *J Endovasc Surg* 1999;6:259–264.
179. Nishanian G, Kopchok GE, Donayre CE, et al. The impact of intravascular ultrasound (IVUS) on endovascular interventions. *Semin Vasc Surg* 1999;12:285–299.
180. van Sambeek MR, Gussenhoven EJ, van Overhagen H, et al. Intravascular ultrasound in endovascular stent-grafts for peripheral aneurysm: a clinical study. *J Endovasc Surg* 1998;5:106–112.
181. White RA, Donayre CE, Kopchok GE, et al. Utility of intravascular ultrasound in peripheral interventions. *Tex Heart Inst J* 1997;24:28–34.
182. White RA, Donayre CE, Walot I, et al. Endoluminal graft exclusion of a proximal para-anastomotic pseudoaneurysm following aortobifemoral bypass. *J Endovasc Surg* 1997;4:88–94.
183. Muller-Hulsbeck S, Schwarzenberg H, Hutzelmann A, et al. Intravascular ultrasound evaluation of peripheral arterial stent-grafts. *Invest Radiol* 2000;35:97–104.
184. Yadav J. Presentation. Annual Scientific Sessions of the American Heart Association, November 9–12, 2003; Orlando, FL.
185. Bosch JL, Tetteroo E, Mali WP, et al. Iliac arterial occlusive disease: cost-effectiveness analysis of stent placement versus percutaneous transluminal angioplasty. Dutch Iliac Stent Trial Study Group. *Radiology* 1998;208:641–648.
186. Hagenaars T, Lim AP. IF, van Sambeek MR, et al. Gamma radiation induces positive vascular remodeling after balloon angioplasty: a prospective, randomized intravascular ultrasound scan study. *J Vasc Surg* 2002;36:318–324.
187. Tegtmeyer CJ, Selby JB, Hartwell GD, et al. Results and complications of angioplasty in fibromuscular disease. *Circulation* 1991;83 [2 Suppl]:I155–I161.
188. Rosenfield K, Schainfeld R, Pieczek A, et al. Restenosis of endovascular stents from stent compression. *Journal of the American College of Cardiology* 1997;29:328–38.
189. Degertekin M, Serruys PW, Foley DP, et al. Persistent inhibition of neointimal hyperplasia after sirolimus-eluting stent implantation: long-term (up to 2 years) clinical, angiographic, and intravascular ultrasound follow-up. *Circulation* 2002;106:1610–1613.
190. Serruys PW, Degertekin M, Tanabe K, et al. Intravascular ultrasound findings in the multicenter, randomized, double-blind RAVEL (RAndomized study with the sirolimus-eluting VElocity balloon-expandable stent in the treatment of patients with *de novo* native coronary artery Lesions) trial. *Circulation* 2002;106:798–803.
191. Sonoda S, Honda Y, Kataoka T, et al. Taxol-based eluting stents from theory to human validation: clinical and intravascular ultrasound observations. *J Invasive Cardiol* 2003;15:109–114.
192. Hansrani M, Overbeck K, Smout J, et al. Intravascular brachytherapy for peripheral vascular disease. *Cochrane Database Syst Rev* 2002:CD003504.
193. Pokrajac B, Wolfram R, Lileg B, et al. Endovascular brachytherapy in peripheral arteries: solution for restenosis or false hope? *Curr Treat Options Cardiovasc Med* 2003;5:121–126.
194. Lerman A, Burnett Jr JC, Higano ST, et al. Long-term L-arginine supplementation improves small-vessel coronary endothelial function in humans. *Circulation* 1998;97:2123–2128.