Atherosclerosis: Pathogenesis, Morphology, and Risk Factors
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Key Points
• Despite improvements in treating symptomatic cardiovascular diseases due to atherosclerosis, prevention remains a key approach to stemming the tide of morbidity and mortality.
• Atherosclerosis is a disease with multiple potential etiologies; therefore, prevention must address the overall risk factor profile.
• Lifestyle therapies such as smoking cessation, weight management, and physical activity are cornerstones of prevention.
• Antihypertensive therapy and lipid modification, especially with the statins, have emerged as clinically sound drug approaches to risk reduction.
• Novel risk factors may help improve risk stratification or identify new targets of therapy.

Background and History
Once considered an irreversible, inevitable consequence of aging, atherosclerosis [from the Greek atheroma, meaning “gruel” and sclerosis, meaning “hardening”] is now recognized as a disease that may be prevented or managed with treatment. Improvements in medical care have reduced morbidity and increased survival following an atherosclerotic event, such as unstable angina, cerebrovascular accident, and myocardial infarction [MI]. However, the successful management of acute coronary syndromes with angioplasty, thrombolytic therapy, and glycoprotein IIIb/IIIa inhibitors does not cure the process of atherosclerosis, and the improved survival has resulted in an increased prevalence of patients who must live with a significant atherosclerotic burden. The complications of atherosclerosis result in sizable health expenditures for the United States. Therefore, prevention remains a critical approach to stemming the disease’s progress.

The decline in age-adjusted morbidity and mortality has increased the presence of vascular disease in patients above the age of 75 years. Epidemiologic studies have analyzed morbidity and mortality in people above the age of 75 years and have determined that approximately 70% of all deaths in this age group are due to cardiovascular disease. Additionally, significant morbidity and mortality due to stroke and congestive heart failure also contribute to the public health burden in the elderly. While the incidence of coronary disease is gradually shifting to an older age group, atherosclerosis remains a major threat to younger individuals. Men younger than 60 years of age have a significant risk for the development of premature vascular disease. Cardiovascular disease can be documented in approximately 30% of men younger than 60 years of age, a rate that is significantly higher than that in age-matched women.1,2 In older women, the morbidity and mortality related to cardiovascular disease is similar to men.3

Effective management for any condition requires a precise knowledge of the pathophysiology of the disease state, sensitive and specific tests for the presence and severity of the disease, and the availability of therapies with demonstrated efficacy. Atherosclerosis is a syndrome with a variety of underlying predisposing causes, and curative therapy is currently not available. However, advances in medical therapy in the treatment of dyslipidemia and hypertension have significantly altered the clinical course of disease and in some cases have resulted in regression of the atherosclerotic process. Additionally, hygienic measures such as smoking cessation, exercise, and weight loss have also proved effective in modifying the risk for cardiovascular disease. The concept of risk factor identification, stratification, and modification has gained considerable clinical importance over the past decade.
The availability of precise diagnostic tests coupled with the development of modulators of the renin angiotensin system, 3-hydroxy-3-methylglutaryl coenzyme A [HMG CoA] reductase inhibitors [or statins], improved antiplatelet therapy, and other advances has contributed to the decline in vascular disease. This chapter discusses the role of risk factor identification and modification as a means to alter the process of atherosclerosis.

Pathophysiology

The response-to-injury hypothesis, originally proposed by Virchow and von Rokitansky and advanced by Ross, extended the injurious role of inflammation as an initial stage of atherosclerosis. The response-to-injury hypothesis postulates that the initiation and progression of occlusive atherosclerotic coronary and peripheral vascular disease involves a nonspecific and stereotypic response incited by endothelial damage or dysfunction. The response-to-injury hypothesis emphasizes the concept of coronary artery disease [CAD] as a syndrome with a multiplicity of potential underlying etiologies that may alter endothelial function. These etiologies include metabolic abnormalities such as hypertension, obesity, dyslipidemia, or diabetes that result in imbalance in lipid permeability, clotting, fibrinolysis, and vascular tone.

Physical damage to the endothelium may occur because of altered shearing forces related to elevated blood pressure, immune-mediated injury, or toxic damage as seen with exposure to tobacco inhalants. In response to these injuries, the endothelium suffers functional abnormalities followed by morphologic changes in the vessel wall that include the deposition of lipids, calcium, and connective tissue.

Endothelial Dysfunction

Dysfunction of the endothelial lining of the vascular system is a preclinical stage of atherosclerosis. The endothelium plays a major role in vascular tone. Nitric oxide is synthesized in the endothelium and is a potent, antiinflammatory vasodilator and antiplatelet agent. Additionally, nitric oxide plays a significant role in reduction of cellular adhesion to the endothelial lining. The endothelium is intimately involved in multiple physiologic functions, including regulation of the movement of lipoproteins across the vessel wall, the balance between thrombosis and fibrinolysis, and as the site of a variety of enzymes involved in the metabolism of triglyceride-rich lipoproteins, in addition to angiotensin-converting enzyme. Platelets bind to the dysfunctional endothelium and smooth muscle cells are activated via platelet-derived growth factors leading to cellular proliferation. The endothelium produces a variety of vasoactive molecules in addition to nitric oxide. The major vasoconstrictors generated by the endothelium are angiotensin II and endothelin. The vasoconstrictors are counterbalanced by nitric oxide, prostacyclin, bradycrin, and other compounds that are either produced directly or act indirectly to alter the tone of the vessel wall. The deleterious effects of the classical CAD risk factors for coronary disease are partially due to their effects on endothelial function. Dyslipidemic patients experience a physiologic shift in endothelial function to a proatherogenic and prothrombotic state characterized by inappropriate vasorestriction, the elaboration of a variety of adhesion molecules, and an imbalance between fibrinolytic compounds such as tissue plasminogen activator and its naturally occurring inhibitor, plasminogen activator inhibitor [PAI-1]. The endothelial dysfunction associated with dyslipidemia may be reversed by statin therapy.

Inflammation

The premise that chronic inflammation may play a role in coronary disease has recently been popularized, although the concept is not new. Leukocytosis has been correlated with atherosclerosis risk in epidemiologic and experimental studies. Histologic studies of occlusive coronary artery lesions have demonstrated increased infiltration of inflammatory cells such as T lymphocytes and monocytes into the plaque with a concentration within areas associated with plaque rupture. Cytokines are associated with the degree of inflammation and regulate the migration of monocytes into the subendothelial space following binding to the endothelium through the elaboration of monocyte chemotactant protein 1 [MCP-1]. The preclinical phase of atherosclerosis is characterized by the attachment of inflammatory cells modulated by the production of vascular adhesion molecules, which localize on the endothelium and bind the circulating cellular elements prior to transmigration into the subendothelial space where conversion to the macrophage occurs. These macrophages express a scavenger receptor capable of recognizing, binding, and internalizing a number of lipoprotein subparticles, especially oxidized low-density lipoprotein [LDL]. Macrophages thus act as localized tissue scavengers and interact with growth factors and chemotactants, such as platelet-derived growth factor and MCP.

The Infection Hypothesis

The role that infection potentially plays in atherosclerosis has been supported by epidemiologic studies and relatively small prospective trials. Helicobacter pylori, cytomegalovirus, and Chlamydia pneumoniae have all been postulated to be associated with increased risk for coronary atherosclerosis. In a post hoc analysis of the Helsinki Heart Study involving 4081 dyslipidemic men, infection by C. pneumoniae was an independent risk factor for the development of CAD. Recent prospective treatment trials have been generally disappointing in the prevention of atherosclerosis by antibiotic therapy. Although other smaller studies have provided evidence of benefit, the bulk of prospective clinical trial data does not support the use of antibiotic therapy in prevention of cardiovascular events in patients with coronary disease [Table 74.1]. However, the possibility that infection may play a role in atherogenesis has not been totally excluded and will require further study.

Smooth Muscle Cell Proliferation

Platelet-derived growth factor-β enhances the proliferation and activation of smooth muscle cells and fibroblasts. Growth factors such as transforming growth factor-β are produced,