Atherosclerotic plaque morphology and coronary thrombi

Allen P. Burke, MD, Andrew Farb, MD, Frank D. Kolodgie, PhD, Jagat Narula, MD, PhD, and Renu Virmani, MD

The concept of plaque vulnerability implies a propensity toward coronary artery thrombosis, and the term *vulnerable* was originally intended to provide a morphologic description consistent with plaques that demonstrate a higher likelihood of rupture.[1-4] However, it is becoming known that the etiology of coronary thrombosis is diverse and can also arise from entities of plaque erosion and calcified nodules. In this report we initially review the evolution of atherosclerosis from early lesions to advanced plaques. Our main objective, however, is to describe in detail the 2 diverse plaque morphologies associated with coronary thrombi and their relationship to risk factors: (1) plaque rupture and (2) plaque erosion. Histologic observations on these acute coronary lesions help explain the events leading to symptomatic coronary heart disease. Characterization of pathologic substrates in vulnerable plaques should allow identification of targets for development of noninvasive imaging strategies.[2] These pathologic substrates often bear characteristic molecular alterations, some of which may be chosen as the appropriate targets. Precise pathologic description is important to understand the molecular basis of lipid accumulation, inflammatory cell infiltration, and proliferation of smooth muscle cells with their migration to the neointima in atherosclerotic lesions.

AMERICAN HEART ASSOCIATION CLASSIFICATION OF ATHEROSCLEROTIC PLAQUES

Early lesions found in the coronary arteries of both symptomatic and asymptomatic patients include adaptive lesions, fatty streaks, and intermediate lesions. These lesions have been comprehensively examined and presented in the American Heart Association (AHA) lesion classification scheme[5] (Figures 1 and 2).

From the Department of Cardiovascular Pathology, Armed Forces Institute of Pathology, Washington, DC.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or reflecting views of the Departments of the Army, Air Force, or Defense.

Reprint requests: Renu Virmani, MD, Department of Cardiovascular Pathology, Armed Forces Institute of Pathology, 6825 16th St, NW, Washington, DC 20306-6000; *virmani@afip.osd.mil.*

J Nucl Cardiol 2002;9:95-103.
43/1/121771
doi:10.1067/mnc.2002.121771

Early Atherosclerotic Lesions

Although the earliest recognizable atherosclerotic plaque is the fatty streak (by gross inspection), some researchers consider adaptive intimal thickening as the initial atherosclerotic lesion. Adaptive lesions occur soon after birth and consist of smooth muscle cells embedded in a proteoglycan-rich matrix. Both fatty streaks and adaptive lesions can be found in all races predominantly in the aorta in the first decade of life. The AHA classification divides atherosclerotic lesions into 6 different types.[5,6] Type I intimal lesions occur mostly in infants and children but are also found in adults. These nascent plaques exist as small yellow dots at the aortic root and are not always grossly visible. By histology, type I lesions consist of lipid-containing foam cells, but macrophages without lipid may also be present.

Type II lesions or fatty streaks grossly appear as yellow streaks, patches, or spots on the arterial intima. Fatty streaks turn red after staining with Sudan III or IV and are commonly referred to as "sudanophilic lesions." Fatty streaks are better defined histologically, as some of these lesions may not be visible grossly. The early fatty streak consists mostly of macrophage-derived foam cells; but not all of the macrophages contain lipid, and smooth muscle cells may also contain lipid. In addition, fatty streaks often contain T lymphocytes and mast cells. Although the majority of lipid is present within cells, a small amount is also found in extracellular spaces. The primary form of cholesterol in fatty streaks is cholesterol ester, accounting for 77% of the total content. The principal cholesterol esters are cholesterol oleate and linolate, representing 35% and 26% of total ester content, respectively.

Fatty streaks are common in the thoracic and abdominal aorta and usually appear in the first decade of life. In the thoracic aorta the site of highest probability of fatty streak formation is midway between the origin of 2

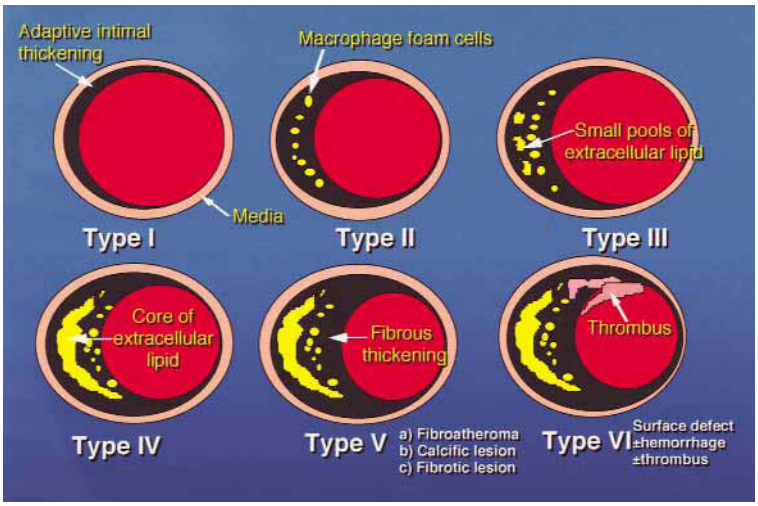

Figure 1. Schematic of the sequence of plaque progression in symptomatic and asymptomatic individuals with coronary atherosclerosis. Types I-IV lesions are similar to those described by Stary et al[5] in the AHA Classification; however, type IV lesions have been modified (see text). Type I lesions are described as adaptive intimal thickening, type II lesions are fatty streaks (lesions with foam cells in the intima), and type III lesions are preatheroma (transitional lesions with small extracellular lipid pools). Notably, type III lesions can have an overlying luminal thrombus, and such lesions occur in young adults. The type IV lesion, or atheroma, is characterized by a necrotic core containing free cholesterol with a well-developed fibrous cap. The type V lesion with a thick, newly formed fibrous cap is called a fibroatheroma (or type Va lesion). In type Vb lesions, the necrotic core or other parts of the plaque are calcified. In type Vc lesions, lipid core is absent and plaque lipid is minimal. Type VI lesions have the additional features of disruption of the plaque (VIa), hemorrhage in the plaque (VIb), or luminal thrombus (VIc); if all 3 features are present, the lesion is termed a type Vabc lesion.

successive intercostal arteries and lateral to them. Similarly, abdominal lesions are found near the ostia of lumbar arteries. The area distal to the flow dividers of the intercostal, lumbar, and distal aorta are usually spared. In the coronary arteries the appearance of the fatty streaks is delayed and begins around 15 years of age.

Type III lesions (also known as intermediate lesions, transitional lesions, or preatheroma) have microscopically visible extracellular lipid pools interspersed with layers of smooth muscle cells.[5] These lesions are usually found near sites of adaptive intimal thickening. The lipid is either membrane bound or free and is located just below the layers of macrophage-derived foam cells. The lipid pools contain more cholesterol, fatty acid, sphingomyelin, lysolecithin, and triglyceride than type II lesions.

Advanced Lesions of Symptomatic Coronary Artery Disease

Type IV, V, and VI plaques constitute the advanced lesions of atherosclerosis, and the term *atheroma* is applied to type IV and V lesions[6] (Figures 1 and 2). The type IV lesion consists of extracellular lipid forming the central portion of a soft core surrounded by macrophage-derived foam cells, which are especially concentrated toward the lumen. The area between macrophage-derived foam cells surrounding the core and the lumen is occupied by smooth muscle cells embedded in a proteoglycan-rich matrix with minimal collagen. Smooth muscle cells are the major cellular constituents of the fibrous cap. Type IV lesions are grossly visible and in young individuals are located at sites of adaptive intimal thickening (ie, at arterial branch points). These eccentric lesions do not result in luminal narrowing and commonly contain vascularization by capillaries in the base and lateral borders of the lipid core. Type IV lesions have been thought to be susceptible to fissuring and may even rupture at the periphery of the lipid core (ie, shoulder region), which contains large numbers of macrophages.

Type V lesions are similar to type IV lesions except for increased fibrous cap thickness overlying the lipid core in the former; these lesions are often referred to as *fibroatheromatous plaques*. Type V lesions may show multilayering of extracellular matrix suggestive of repeated disruption and thrombosis. The lipid core may be small and the overlying fibrous cap replaced by collagenous connective tissue that may have resulted from organized mural thrombi and resorption of the lipid core. In some type V lesions the lipid core or other areas of the plaque are calcified, which may occur as a result of cell death. Type VI lesions have many similarities to types IV and V. Type IV and V lesions that show disruption of the