Pathogenesis of Atherosclerosis and Vulnerable Plaque

E. Falk, M.D., Ph.D. [1]
[1]Aarhus University Hospital, Aarhus N., Denmark

Atherosclerosis is a systemic, lipid-driven inflammatory disease of the arterial wall leading to multifocal plaque development. Most plaques remain asymptomatic (subclinical disease), some become obstructive (stable angina), and a few, if any, become thrombosis-prone (vulnerable) and lead to atherothrombotic events such as heart attack and stroke. Although relatively rare, vulnerable plaques in coronary and carotid arteries are the main cause of death and severe disability not only in affluent countries but worldwide.

Vulnerable plaques: The great majority of symptomatic coronary thrombi (~75%) are caused by *plaque rupture*. The remaining thrombi are caused by less well-defined mechanisms of which socalled "plaque erosion" is the most common type. By inference, there are two major types of vulnerable plaques, rupture-prone and erosion-prone, that are presumed to look like the corresponding thrombosed plaques, just without rupture and thrombosis. The prototype of a presumed rupture-prone plaque contains a large and soft lipid-rich necrotic core covered by a thin and inflamed fibrous cap. Associated features include big plaque size, expansive remodeling mitigating luminal obstruction (mild stenosis by angiography), neovascularization (angiogenesis), plaque hemorrhage, adventitial inflammation, and a "spotty" pattern of calcifications. Although the macrophage density in ruptured caps is high, whole-plaque macrophage density rarely exceeds a few percents because ruptured caps are tiny.

Vulnerable plaques of the erosion-prone type are heterogeneous and defined only by their fate (thrombosis, mostly mural). The surface endothelium is missing, but whether it vanished before or after thrombosis remains unknown. No distinct morphological features have been identified but, in general, eroded plaques with thrombosis are scarcely calcified, rarely associated with expansive remodeling, and only sparsely inflamed. So, irrespective of plaque type, it is a misconception that vulnerable plaques are heavily inflamed. Advanced plaques, including those that appear vulnerable, are in general hypocellular and consist mainly of fibrous tissue, necrosis, and calcifications.

Determinants of vulnerability: Plaque rupture requires the presence of a lipid-rich necrotic core covered by a thin fibrous cap. The size of the necrotic core and the thickness of the fibrous cap appear to be the two major structural determinants of vulnerability. The fibrocellular part of the plaque located between the necrotic core and the lumen is called the *fibrous cap*. It is extremely thin in coronary plaque rupture. Assessed by microscopic examination postmortem, ruptured caps were usually <65 microns thick. Assessed by optical coherence tomography in vivo, the mean thickness was only 49 microns. If the fibrous cap is thin, the plaque is called a *thin-cap fibroatheroma* (TCFA). In TCFA, the necrotic core occupies ~23% of plaque area. Thin fibrous caps are usually heavily inflamed (macrophage density ~14%), particularly those that have ruptured (macrophage density ~26%), but because they are thin, their ability to accommodate macrophages are limited. Apoptosis is common at the site of fibrous cap rupture, usually confined to macrophages because the vascular smooth muscle cells (SMCs) already have vanished when rupture occurs. With their ability to synthesize extracellular matrix, including collagen, SMC apoptosis is associated with impaired healing and repair, increasing the risk of plaque rupture.

Atherosclerosis is an innate inflammatory disease in which smoldering inflammatory activity is not confined to just a few atherosclerotic lesions but is present, more or less, in all such lesions throughout the body. In contrast, vulnerable plaques are relatively rare, and inflammation may play a causal role in plaque rupture only if located within a thin fibrous cap, i.e. the microstructure of the plaque needs to be permissive for rupture. Thus, although plaque inflammation may be useful as a marker of disease activity, it is probably not useful as a stand-alone marker for plaque vulnerability.

Atherothrombosis in carotid arteries: Similar to coronary atherosclerosis, plaque rupture is by far the most common cause of symptomatic thrombosis in carotid atherosclerosis, but the thrombus is more often nonocclusive and prone to embolize, often prolonged because of slow-healing plaque ulceration. Intraplaque hemorrhage is common. Carotid plaques, including those that rupture, are rarely heavily inflamed. The critical thickness for a rupture-prone cap is greater for carotid plaques than for the much smaller coronary plaques, but a relatively thin cap is most critical for rupture in both arteries. In one study, the mean fibrous cap thickness in carotid plaque rupture was found to be nearly three times greater than in coronary plaque rupture (72±15 microns *versus* 23±17 microns; mean±SD), and the macrophage density within ruptured caps was lower (13.5±10.9% *versus* 26±20%).