Vulnerable Atherosclerotic Plaque
A Multifocal Disease
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The recent proliferation of invasive and noninvasive techniques to locate vulnerable atherosclerotic plaques raises important questions. Will such techniques add useful prognostic information? If so, will the information prevent myocardial infarction, stroke, or death in at least some patients at risk? Will it lead to new research advances? Will the benefits justify the costs?

Plaque Progression: Often Abrupt, Rarely Predictable

Some facts are now certain. First, plaque progression and clinical outcome are not always closely related, and each is poorly predicted by clinical and angiographic variables.1–4 Second, many plaques progress episodically because of episodes of thrombosis triggered by rupture, erosion (denu- dation), or occasionally endothelial activation or inflammation.5,6 Unless there is a relatively hypercoagulable state, at least some thrombi remain mural rather than occlusive and produce few if any symptoms unless they embolize7; and if lysis is incomplete and followed by re-endothelialization, the result is a plaque growth. Another mechanism of rapid plaque growth is hemorrhage into the plaque, which is particularly important in the pathogenesis of carotid artery rupture.8,9 Still other plaques develop foci of rapidly proliferating smooth muscle cells.10

Independent Progression of Individual Plaques: Third, plaques within a given patient often progress largely independently.11 This frustrating unpredictability of patient outcomes—even in patients without heart failure or arrhythmias (whose prognosis reflects variables outside the scope of this review)—is probably due in part to fluctuation of risk factors and “triggers,” eg, day-to-day changes in diet, activity, stress, cold weather, pollution, smoking, infection, hydration, and blood pressure. Nevertheless, independent plaque behavior in a given patient must be due in large measure to the marked heterogeneity of plaque histology and to differences in the physical forces to which plaques are subjected.12,13

Vulnerable Plaque Versus Stenotic Plaque

In the past decade, it has become clear that most plaques that underlie a fatal or nonfatal myocardial infarction are, as shown by angiography, less than 70% stenosed. Approximately 60% are caused by rupture of plaques with a large, thrombogenic core of lipid and necrotic debris (including foci of macrophages, T cells, old hemorrhage, angiogenesis, and calcium). The ruptured cap is thin, presumably because macrophages digest it as they cross into and out of the plaque, and because smooth muscle cells (which synthesize the cap) have become sparse because of senescence or apoptosis caused by inflammatory cytokines.

Plaque Inflammation

Another 30% to 40% of coronary thrombi overlie plaques denuded of endothelium, and many if not most of these have luminal inflammation.14,15 Activated T cells in the non-culprit arteries and systemic circulation of patients with unstable
angina, together with recent demonstrations that serum levels of C-reactive protein (CRP) predicts the risk of myocardial infarction (MI) or stroke better than total and low-density lipoprotein cholesterol levels, help explain why techniques such as thermography to detect foci of plaque inflammation before the development of thrombosis have been developed.

However, the lack of data on the natural history of such plaques poses problems. Does everyone with coronary artery disease have vulnerable plaques, or just a subset, such as those with unstable angina and/or elevated serum CRP levels? Do all of these plaques rupture, erode, or thrombose? Do some quiesce or heal? Can these plaques be localized noninvasively or will catheterization be required? Although an elevated serum CRP does not distinguish coronary from aortic, carotid, or peripheral disease (or from infection, malignancy, trauma, or other causes of inflammation), would it be sufficient for screening purposes to combine serum CRP values with some noninvasive techniques such as electron beam computed tomography (EBCT) coronary calcium score?

**Multifocal Nature of Vulnerable Plaques**

Recent studies have emphasized that, by some criteria, many unstable patients have a second or even a third vulnerable plaque, and have called for an emphasis on proven systemic therapies, such as a Mediterranean diet, statins, angiotensin-converting enzyme (ACE) inhibitors, and clopidogrel, rather than unproven approaches, such as stenting. Another promising approach is vaccination against influenza. The recent finding that plaques with superficial inflammation are a strong predictor of vulnerable plaques has led to the development of ultrasound catheters. Thermal heterogeneity is found in nearly all patients with an acute MI. Clinical studies suggest that many MI, strokes, and deaths may be avoided by influenza vaccination.

**Clinico-Pathological Correlation**

Nevertheless, we believe that finding and treating individual vulnerable plaques may also prove useful. Our rationale begins with the fact that, in autopsy studies of victims of fatal MI, a second occlusive thrombus is found in 6% to 16% of victims, though most of these individuals have a second vulnerable plaque (rarely three). Approximately half of these have rupture or erosion with a mural (non-infarct-related) thrombus. In patients with stable symptoms, arterial inflammation is not diffuse, and in these patients most plaques are predominantly fibrotic. Even a study that reported diffuse vascular inflammation in these patients reveals, in its table, that only 2.5% of plaques had moderate or marked infiltration by both macrophages and T cells.

**Angiographic Studies**

By coronary angiography, progression of stenoses over 2 years was noted in 22% of patients with angina pectoris, even in the pre-statin era. Patients with progression averaged only 1.1 progressing lesion, which suggests that simultaneous progression of 2 plaques must be rare.

**IVUS Studies**

The finding of more than 1 ruptured or vulnerable plaque in patients with MI or unstable angina is also supported by a recent intravascular ultrasound study by Riofoul et al., who found 2 or more plaque ruptures in 79% of patients with acute coronary syndromes. However, another study described a single plaque rupture in half of patients who presented with unstable angina.

**Angioscopic Studies**

Angioscopy almost always reveals only 1 thrombus in patients with an MI. However, yellow plaques, which have a high risk of progression to rupture, are found in some patients with stable angina, most patients with unstable angina, and nearly all patients with an acute MI.

**Thermography Studies**

The recent finding that plaques with superficial inflammation are warmer than other plaques whereas normal arteries are uniform in temperature has led to the development of thermography catheters. Thermal heterogeneity is found in some patients with stable angina and in almost all patients with unstable angina, with 2 or even 3 hot plaques being present in patients with an acute MI. Interestingly, levels of serum CRP were not well correlated with the number of hot plaques, and most patients with stable angina and 1 hot plaque had a normal serum CRP level. In the only follow-up study reported to date, thermal heterogeneity was a strong independent predictor of adverse events.

**Needed: Clinical Trials of New Techniques For Detecting Vulnerable Plaques**

Because not all ruptured or eroded plaques are yellow, warm, calcified, etc, it is logical to ask what combination of new techniques might be optimal for risk stratification. The ideal approach would provide both anatomic and functional data.
Plaques at greatest risk for rupture should have an inflamed, thin (or fissured) cap, a large lipid core, and high wall stress (ie, large lumen). Those at risk of erosive thrombosis would have an irregular or denuded inflamed lumen, and thrombogenic slow flow due to a stenosis upstream or downstream. Patients with either of these types of plaque would be at higher risk if they are in a hypercoagulable state or if the lesion is in the proximal left anterior descending coronary artery, particularly if collaterals are inadequate.

Clinical trials are likely to demonstrate that such plaques can be detected with some combination of MRI or computed tomography (CT) with contrast, angiography, thermography, ultrasound or optical coherence tomography (OCT) (either of which could incorporate elastography or integrated backscatter), near-infrared spectroscopy, and/or angioscopy. Such an approach would be expensive, but could prove useful. For example, if a patient is found to be at greater risk than predicted by office or bedside techniques, including serum CRP level, this information may lead the patient to reschedule a physically or mentally stressful task in lieu of rest, or of a critical family meeting or reconciliation. Awareness of vulnerability may also improve adherence to diet and medications, as well as influencing the physician’s treatment goals as to weight, blood pressure, lipids, glucose, and even frequency of office visits. In particular, the presence of vulnerability may merit multiple therapies, such as various combinations of aspirin with warfarin or clopidogrel, ACE inhibitors with β-adrenergic blockers, statins with niacin, fibrates, resins, etc. Finally, as statins may not reduce –

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