Finding Vulnerable Atherosclerotic Plaques
Is It Worth the Effort?

Mohammad Madjid, Alireza Zarrabi, Silvio Litovsky, James T. Willerson, Ward Casscells

Abstract—Techniques to identify and treat vulnerable plaques are the focus of enormous research. Some have questioned the benefit of locating individual vulnerable plaque in a multifocal disease. On autopsy, it is found that most deaths are caused by thrombotic occlusion of a single plaque; simultaneous occurrence of 2 occlusive thrombi is rare, but a second vulnerable plaque is common, particularly in acute myocardial infarction (MI). Angiographic progression is poorly predicted by risk factors, and angiographic progression is a weak predictor of MI or death. Intravascular ultrasonography (intravascular ultrasound [IVUS]) studies find plaque rupture in most MI patients and in approximately half with unstable angina, but in only a minority of patients with stable angina. IVUS identifies a second vulnerable plaque in many patients with unstable angina, and in most MI patients. Angioscopy reveals a very low incidence of a second vulnerable plaque compared with angiography and IVUS, but identifies additional yellow plaques in many patients with stable angina and in most patients with unstable angina or MI. Using thermography catheters and a temperature cutoff of 0.1°C, approximately half the patients with stable angina have >1 hot lesion; however, if the cutoff is 0.2°C, only ~15% have a second hot lesion. New imaging techniques may detect additional characteristics of plaques and new predictive models may assess the risk of vulnerable plaques and patients. This approach enables physicians to “buy time” by application of local therapies until systemic therapies stabilize plaques. This may also reduce the risk in subjects in whom systemic therapies do not work. (Arterioscler Thromb Vasc Biol. 2004;24:1775-1782.)

Key Words: plaque rupture ■ atherosclerosis ■ stents ■ coronary imaging

Coronary heart disease is a leading cause of death in the United States, accounting for >500 000 lives each year.1 Atherosclerosis is the underlying mechanism for unstable angina, myocardial infarction (MI), and sudden cardiac death. Luminal narrowing of arteries caused by atherosclerotic plaque enlargement causes the chronic ischemic manifesta-
tions of coronary heart disease, whereas superimpositions of thrombi over the plaques lead to acute coronary syndromes. To date, angiography has been the method of choice for detecting these problematic arterial lesions. However, this diagnostic technique, which approximately compares the degree of stenosis of arterial lesions relative to the proximal segments of the artery, does not provide insight into the disease state within the artery, and often fails to detect those lesions prone to thrombosis.

A series of landmark angiographic studies in the mid 1980s demonstrated that nearly two-thirds of all MI originate at atherosclerotic lesions that lack hemodynamic significance.2–6 Unfortunately, these “culprit” lesions, which have been termed vulnerable plaques, are undetectable using routine clinical methods of disease evaluation (eg, electrocardiography, angiography, stress test). Of utmost importance is the need to develop new diagnostic techniques for detecting vulnerable plaques. Several studies have shown that some patients may have >1 vulnerable plaque. This has led to the debate on whether it is justified to identify vulnerable plaques.

Reported herein, we review the currently available evidence implicating vulnerable plaques in the development of coronary events and disease progression. For the purpose of this report, the term vulnerable plaque will be used to describe plaques prone to disruption and/or thrombosis. We review emerging techniques for lesion detection and consider the benefits of detecting individual vulnerable plaques and whether focal and/or systemic therapies will be of value.

Pathology of Plaque Rupture and Erosion
Atherosclerosis begins as fatty streaks and over time progresses toward more advanced lesions. Rupture of atherosclerotic plaques accounts for nearly two-thirds of all coronary deaths, and plaque erosion accounts for the majority of the remaining cases. Their underlying pathology is markedly heterogeneous, but the ruptured plaques typically have a large core of free cholesterol, necrotic foam cells, cholesterol crystals, hyalinized hemorrhage, calcification, angiogenesis, and inflammation.7 The fibrous cap is thin (50 to 100 micrometers) and deficient in the matrix-synthesizing smooth muscle cells. Almost all ruptured plaques contain numerous macrophages whose matrix metalloproteinases can digest the cap. In contrast, the eroded plaques are denuded of endothelium and have varying degrees of inflammation and superficial ulceration, which promote thrombosis.8 Inflammatory cells play a major role in initiation and progression of the atherosclerosis, and also in the development of its acute complications, by releasing different pro-inflammatory and pro-thrombotic cytokines.

Most ruptured plaques have foci of hemorrhage of varying ages, at varying stages of organization and fibrosis, suggesting discrete episodes of rupture or erosion leading to thrombosis, followed by partial lysis, then re-endothelialization. Serial angiographic studies also suggest that episodic plaque growth is more common than continuous gradual growth, and that many such episodes are often asymptomatic.9 The fact that some acute thrombi remain mural, whereas others progress to complete occlusion, is probably attributable to differences in coagulability. Conditions that favor thrombosis include differences in smoking, hydration, hormones, catecholamines, fibrinogen, cholesterol, erythrocyte count, leucocyte count, platelet count, protein S, and protein C (including mutated protein C, such as factor V Leiden, etc), and local concentration of thromboxane A2, serotonin, ADP, and tissue factor.10 Another likely reason is low flow caused by upstream or downstream stenosis (whether fixed or vasospastic), which promotes thrombosis.11

Techniques for Identification of Vulnerable Plaque
The natural history of vulnerable plaques is obviously difficult to infer from autopsy studies, and angiography has its
limitations. It correlates only modestly with other measures of ischemia, and its angiographic progression is poorly predicted by risk factors and angiographic variables. Moreover, angiographic progression is a weak predictor of MI or death (relative risk = 2.3). Even a wide array of clinical and angiographic factors, taken together, have been disappointing in their ability to predict clinical events. Hence, there is intense interest in developing new ways to identify vulnerable plaques by means of new risk factors, such as C-reactive protein (CRP), myeloperoxidase (MPO), lipoprotein-associated phospholipase A2, and pregnancy-associated plasma protein A, and to identify vulnerable plaques by noninvasive means, such as magnetic resonance imaging (MRI), computed tomography (CT), and intravascular methods, such as ultrasound (and the related techniques of integrated backscatter and elastography), thermography, near-infrared spectroscopy, angioscopy, and optical coherence tomography (Figure).14

**Single Versus Multifocal Nature of the Disease**

**Autopsy Studies**

Will it help to identify the individual vulnerable plaque in a disease that is often multifocal or even diffuse? Most deaths are caused by thrombotic occlusion of a single plaque. For example, Levin and Fallon described a careful postmortem angiographic and histological study of patients with fatal MI and did not describe multiple plaque ruptures or multiple ulcerations. In a dozen autopsy series of patients with sudden coronary atherosclerotic death from 1970 to 1990, Liberthson’s study was the only one that described any second thrombosis. These were noted in 16% of the autopsies. Ridolfi and Hutchins studied 494 large fatal myocardial infarcts, almost all of which were caused by thrombotic occlusion of an atherosclerotic coronary artery. A second area of ulceration was seen “frequently,” but no second thrombus was noted. Horie described 108 autopsies with an occlusive coronary thrombus found in 80%. Of these, 91% were complications of a ruptured plaque. Only 6% of patients had a second thrombus. Qiao and Fishbein studied patients with fresh coronary thrombosis and found a second thrombus in 14%. In a series of 47 sudden cardiac deaths in those who underwent autopsy Falk, 2 patients had a second occlusive thrombus, although there were 63 foci with rupture and no thrombosis.20

In recent years, the incidence of multiple thrombosis has been lower, but the incidence of plaque rupture or vulnerable plaque (defined as a large atheroma with a thin, inflamed cap, or an erosion) has been higher. This trend may be caused by the increasing use of heparin, aspirin, ticlopidine, and clopidogrel. For example, in a series of 168 sudden coronary deaths described by Davies, 73% of the victims had a mural or occlusive thrombus. Fissuring without thrombosis was seen in 7.7%. Among age-matched controls without clinical coronary disease, 8.7% exhibited fissuring without thrombosis, and fissuring was found in 17% of coronary patients who died of other causes. Five percent of these patients had a thrombus, which must have been clinically silent if the death was truly caused by noncoronary cause. In this series, however, no patient with a second thrombus was described.

In a series of sudden coronary deaths caused by plaque rupture and thrombosis reported by Farb, each victim had a second vulnerable plaque (defined as a thin cap overlying an atheroma; other high-risk features, such as inflammation, hemorrhage, calcification, angiogenesis, large core size, or fissuring, were not required). Burke studied 113 victims of sudden cardiac death, 59 of whom had coronary thrombosis. Rupture was found in 41 of these and 18 others were eroded. There were 79 plaques described as vulnerable because of a thin cap with macrophage infiltration, with or without rupture. These plaques were not thrombosed. Frink reported a series of 83 patients with sudden cardiac death in whom 211 disrupted plaques were found, 102 of which had luminal thrombosis. A study of 298 fatal MI by Arbustini found that 2% had no thrombus, 88% had a single thrombus, 9% had 2 thrombi, and 1% had 3 thrombi.

In some of these series, a distinction was made between a luminal versus occlusive thrombus and between fresh versus organizing thrombus. Most of the second thrombi were mural or recent rather than occlusive or acute. In other words, simultaneous occurrence of 2 occlusive coronary thromboses is rare.

To summarize dozens of previous studies, most fatal infarcts and sudden deaths are caused by coronary thrombosis or by rupture or erosion of a single plaque, and most have an additional 1—and occasionally 2—vulnerable plaques. Many of the latter exhibit rupture, usually with mural rather than occlusive thrombus.

**Angiography Studies**

Angiographic series likewise suggest that a second acute thrombus is rare, but a second vulnerable plaque is common, particularly in patients with acute MI. Studying angiographic progression in symptomatic patients, Shub noted progression over a 2-year period in only 22% of lesions, with an average of 1.1 progressing lesions per patient. This suggests that simultaneous lesion progression is uncommon. Ge et al found no instance of a second vulnerable plaque in an angiographic and ultrasound study of patients with stable and unstable angina pectoris. In a study of asymptomatic angiographic progression over an 8-month period in patients with stabilized angina awaiting surgery, Kaski et al reported that among the 24% of patients who showed progression, only 1 lesion progressed in each patient. Subsequently, the same group reported an average of 2.6 angiographically complex plaques per patient with unstable angina. In that study, a sensitive but nonspecific definition of angiographic complexity was used: either irregularity or angiographic thrombus. Angiographic findings in 350 patients with non–Q-wave MI were described by Kerensky et al. Fourteen percent had >1 culprit lesion. Goldstein et al reported a large series of patients with ST-segment elevation/Q-wave MI. Forty percent had a second vulnerable plaque, as defined by 2 or more of 4 criteria: slow flow, ulceration, irregular surface, or angiographic thrombosis. If those characteristics were evenly distributed, then ~20% of the patients had a second thrombus.
Intravascular Ultrasound Studies
Intravascular ultrasound (IVUS) is better than angiography at measuring the lumen area and can also detect calcification in some areas of low density in the plaque. With recent advances in radiofrequency signal analysis, integrated backscatter may be able to distinguish the very-low-density fatty areas from areas of hemorrhage. Ultrasound is also able to detect evidence of plaque remodeling and can identify large ruptures and clots, although it is not as sensitive as angiography in the detection of mural thrombosis or fissures. IVUS studies find plaque rupture in most patients with MI and in approximately half the patients with unstable angina or MI but in only a minority of patients with stable angina. Patients with unstable angina or MI have been found to have, in many or most cases, a second vulnerable plaque that is detectable by IVUS. Unfortunately, IVUS cannot easily distinguish caps of 0.4 mm in thickness from those that are 0.1 mm or less in thickness. This limitation may be, in the near future, addressed indirectly by the technique of elastography (also known as palpography), which can detect systolic dimpling of the thin-capped soft plaque.

Optical Coherence Tomography Studies
Like ultrasound, optical coherence tomography (OCT) shows an image from a reflected wave, but because it uses near-infrared (shorter wave lengths than ultrasound) and interferometry, OCT yields much finer spatial resolution (≈10 to 20 micrometers). Unfortunately, OCT requires inflation of a proximal balloon to obstruct blood flow (to flush the artery to obtain a clear field of view). This could cause ischemia and/or vessel injury, and the balloon precludes assessment of the proximal segments, as with angioscopy.

Angioscopy Studies
Intracoronary angioscopy is superior to angiography and ultrasound in detecting fissuring or thrombus, but it characterizes only the luminal surface and requires a proximal balloon. However, useful information has come from angioscopic clinical research. Eighty to 85% of plaques thought to be the culprit in MI are found by angioscopy to be thrombosed, versus half of those with unstable angina. In contrast, only 15% of those with stable angina have a thrombus by angioscopy. Most of the thrombosed plaques have a complex topography, and most complex plaques are yellow. One study suggests that a bright, glistening yellow color is a specific predictor of infarction, although the sensitivity was only ≈50%.

With regard to the prevalence of a second complex or thrombosed lesion, Sherman et al described none, whereas Uchida et al found that ≈20% of patients had a second yellow plaque, and nearly 10% had a second ulcerated plaque. Asakura et al found a second thrombus in 2% of the patients with MI, but most studies do not mention a second complex or thrombosed lesion. All of the many angioscopic series describe a very low incidence of a second disrupted plaque compared with angiographic and IVUS studies, but angioscopy identified additional yellow plaques in many patients with stable angina and most patients with an unstable angina or MI.

Thermography Studies
Normal arteries are uniform in temperature, but in living atherosclerotic plaques, there are hot spots that overlie regions where inflammatory cells are dense or close to the lumen surface. Further evidence that it is the inflammatory cells that generate the heat is suggested by the diminution in temperature by indomethacin in organ culture and by statins in a clinical series. Moreover, thermal heterogeneity correlated with levels of CRP. However, this could be a spurious finding, probably because patients with little thermal heterogeneity in the coronaries can have an elevated CRP caused by inflamed plaques elsewhere, or caused by arthritis, infection, trauma, or malignancy. In contrast, some patients have hot spots in their coronary arteries despite undetectable low levels in high-sensitivity CRP assays. The greatest thermal heterogeneity is found in patients with acute MI. Those with unstable angina pectoris have less heterogeneity, and patients with stable angina have the least. Yet among patients undergoing a percutaneous coronary intervention, those who do have hot plaques have the highest rate of adverse clinical events, according to Stefanadis et al.

The number of hot plaques depends on the definition (the arbitrary temperature cutoff) such that if the temperature cutoff is 0.1°C, approximately half the patients with stable angina have >1 hot lesion; whereas if the cutoff is 0.2°C, only ≈15% have a second hot lesion. Larger temperature differences are found in the Stefanadis study patients probably because—compared with the reports from New Zealand and Europe—most were not using aspirin and statins and had higher CRP levels. Also, Stefanadis used a large, insulated thermistor that occluded flow, minimizing the dilutional cooling by the flowing blood.

Value of Systemic Markers of Inflammation
Maseri et al and other groups have described activation of circulating T lymphocytes in patients with unstable angina or MI. In patients with fatal MI, Spagnoli et al found nearly as many macrophages in the nonculprit artery as in the culprit artery, although the latter had more activated T cells, and numerous studies have now documented that using a sensitive assay, the inflammatory serum marker, CRP, is elevated in patients with unstable angina and more so with MI. Moreover, the levels are predictive of risk of MI in every category of patients studied to date. The caveat is that patients with renal disease, infection, cancer, autoimmune diseases, liver and kidney disease, and trauma are excluded because these problems can elevate serum CRP levels.

Buffon et al found the gradient (from coronary ostium to sinus) in neutrophil MPO was similar across “culprit left anterior descending coronary artery (LAD)” and “nonculprit” coronary stenoses in other vessels. They concluded that plaque inflammation is diffuse. However, a few caveats should be noted. First, neutrophils (the main source of MPO)
are rare even in inflamed plaques, moderately numerous in ruptured plaques, and omnipresent in MI plaques and reperfused microvessels. Buffon’s myeloperoxidase may have come mainly from micro-infarcts, which are expected, because the study included patients with angina at rest. Thus, their data may relate more to thrombosed or embolizing plaques than to vulnerable plaques. Second, the great cardiac vein does not receive blood exclusively from the LAD but from the entire left ventricle, particularly when there is a tight stenosis in the LAD that leads to the development of collaterals. Finally, noncoronary sites of inflammation may contribute to circulating levels of MPO.

If Most Patients Have Multiple Inflamed Plaques Detectable by CRP, Why Locate Vulnerable Plaques?
The lesions at higher risk have not only inflammation but also a thin and/or fissured cap. The risk is higher still if the plaque has a large lipid core and a history of rupture or remodeling. Moreover, by LaPlace’s law, the wall stress (and presumably the risk) is higher if the lumen is large. Furthermore, the cap can be vulnerable if the endothelium is prothrombotic (“activated”) or empty (“denuded”), or if the surface is irregular, which promotes thrombosis by means of the reduced shear rates and increased stasis.

Thrombosis is also promoted if there is an upstream or downstream flow-limiting stenosis. Moreover, the lesion has a greater capacity to cause clinical ischemia if it is proximal, because of the larger territory it serves. In addition, if collateralization is absent or inadequate, as is usually the case in patients with MI, the risk of infarction is obviously greater.

The severity of inflammation is probably critical, as well. van der Wal et al, who described inflammation as being widespread, nevertheless found that only 2.5% of plaques had moderate or severe infiltration by both macrophages and T lymphocytes, which regulate macrophages. Because macrophages can be activated by T cells, and because markers of T-cell activation in the coronary circulation identify patients at high risk for MI or death, it is likely that the lesions at highest risk are those with activated T cells and activated macrophages.

These features are likely to be detectable in the near future by some combination of CT, MRI, angiography, angioscopy, IVUS (particularly with elastography and/or integrated backscatter), OCT, thermography, near-infrared spectroscopy, or molecular imaging. Using a more complete list of predictive criteria will increase the sensitivity and specificity of detecting vulnerable plaques. A gradient of risks will result and will permit a cutoff based on whether the risk of that plaque exceeds the risk of therapy. These criteria could provide a relative risk for a given plaque. The absolute risk could then be estimated by summing the number and vulnerability of each individual plaque and adding the patient’s history and symptoms, family history, or genetic information, together with data from the physical examination, electrocardiogram, exercise test, and laboratory findings, such as risk factors for thrombosis and inflammation (including genetic polymorphisms). Long-term outcome studies are needed to estimate and validate the absolute risk score.

Even if the Number of Vulnerable Plaques Adds Prognostic Data, How Will This Help the Patient?
The usefulness of locating vulnerable plaque is unproven, but it must be recognized that prognosis is valuable to the patient, who may defer travel, relocation, or elective surgery, to cite just a few examples. Prognosis may prompt a patient to delay a major purchase or new venture, but not other things, such as a family meeting, a reconciliation, or even a last will and testament. More importantly, information about plaque vulnerability may lead to a life-saving change in diet, activity (eg, initial rest, followed by a gradual exercise program), or goals (eg, better management of low-density lipoprotein, blood pressure, and weight). This may influence the number and dose of medications, the patient’s adherence to a medical regimen, and the frequency of monitoring.

Treatment
Most importantly, vulnerability may be reduced by broader uses of existing therapies, such as the combination of aspirin, clopidogrel, and/or warfarin, of angiotensin-converting enzyme inhibitors (or angiotensin-receptor blockers), plus beta blockers and nitrates. The choice of beta blockers may be particularly important, because these are likely to lower the rate-related risk of rupture and, should ischemia develop, the myocardial contractility, the loss of diastolic filling time, and the vulnerability to ventricular fibrillation. Other patients may be treated not only with statins but also with niacin, fribates, and a resin (or ezetimibe) or newer agents such as cholesterol ester transfer protein inhibitors and agents that raise high-density lipoprotein.

Administration of high-density lipoprotein cholesterol or apolipoprotein (Apo) A-I Milano are other potentially promising approaches toward stabilizing vulnerable plaques. Infusion of recombinant ApoA-I Milano–phospholipid complexes produces rapid regression and stabilization of atherosclerotic plaques in animal models. A recent human clinical trial demonstrated significant regression of coronary atherosclerosis as measured by IVUS after infusion of a recombinant ApoA-I Milano–phospholipid complex. Low-density lipoprotein apheresis, already used in some patients with familial hypercholesterolemia, is yet another possibility.

In addition to statins and angiotensin-converting enzyme inhibitors, other potential anti-inflammatory and antiproliferative treatments include corticosteroids, cyclosporin, antithymocyte globulin, and rapamycin. Short courses may be well-tolerated.

Numerous novel anti-inflammatory agents and local gene therapies are in development, targeting tumor necrosis factor-α, interferon-γ, monocyte chemotactic protein-1, vascular cell adhesion molecule 1 (VCAM1), and NF-κB. Other gene therapies are directed at enhancing local culprit lesions’ availability of prostacyclin or tissue factor pathway inhibitor (tissue factor pathology inhibitor), transforming growth factor-β1, or interleukin-10. Even a simple warm infusion
may be helpful, because there is evidence that gentle heating broadly downregulates the inflammatory process.\textsuperscript{71}

However, long-term anti-inflammatory therapies are likely to be contraindicated because of the risks of infection, hypertension, renal failure, impaired healing, etc.\textsuperscript{72,73} Thus, it may be important to try to eliminate the antigens, such as oxidized low-density lipoprotein cholesterol, and infection (such as influenza).\textsuperscript{74}

Our experience is that many doctors and patients are unaware of the proven benefits of a Mediterranean-type diet and of cost-effective interventions, such as influenza vaccine, in reducing cardiovascular and all-cause mortality.\textsuperscript{75} However, even these approaches are not likely to stabilize all plaques quickly enough to eliminate the need for interventional therapies, and some patients cannot tolerate polypharmacy. Higher doses of available drugs or novel therapies may work faster in these circumstances.

Clinical trials are needed to test the hypothesis that some patients with vulnerable plaques benefit from stenting of a lesion that is only 50\% stenosed and not flow-limiting, but which has vulnerable features. Or a longer stent may be chosen to dilate not only the ischemia-causing stenosis but also the adjacent vulnerable lesion. Because statins do not reduce mortality for several months, local interventional therapies are likely to be needed to “buy time” until the medical regimen confers significant protection. Even if occlusion of the 95\% LAD stenosis rarely causes MI (because of extensive collaterals), opening that segment may ensure collateral support in case the right or circumflex coronary artery disease? Circulation. 1988;78:1157–1166.


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**References**


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