CARDIOLOGY Rounds®

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Anticipating Acute Coronary Syndromes: Identifying Vulnerable Plaque in Vulnerable Patients

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The manifestations of atherosclerotic coronary artery disease (CAD) can be classified into those that arise from stable plaques and those that arise from unstable plaques (Figure 1). Stable plaques may not cause clinical symptoms or, in some patients, may lead to the symptom of stable angina. Stable plaques and stable angina are conditions that are associated with low mortality and excellent long-term clinical outcome. In contrast, the consequences of unstable plaques are much more severe. In fact, approximately one-third of acute plaque occlusions result in sudden cardiac death without the opportunity for intervention. Even in those patients presenting to hospital with an acute coronary syndrome, the short-term mortality risk is substantially increased by the plaque rupture event.[1] In recent clinical trials, the one-year mortality of patients with acute coronary syndrome is around 10%.[2]

Although contemporary therapies for acute coronary syndromes have been successful in reducing the risk in these patients, a potentially more efficient strategy is to prevent the rupture of vulnerable plaque in the first place. This would be particularly true for patients who are at risk of sudden cardiac death who would be unable to present to hospital. This issue of *Cardiology Rounds* presents a review of the pathophysiological basis of plaque rupture, current invasive and noninvasive imaging techniques and biomarkers for assessing vulnerable plaque, a risk stratification approach, and therapeutic considerations for patients with vulnerable plaques.

It is a common clinical observation that some patients can have extensive CAD and have stable angina until an advanced age, while others with minimal disease may present with a ruptured plaque and an acute coronary occlusion at an early age

What dictates the outcome in a given patient is currently unknown. Our conventional tools for predicting which patients are at risk for CAD (eg, the Framingham risk equation) are limited. In fact, the outcomes in the Framingham equation include both stable angina and acute myocardial infarction (MI), despite their markedly different clinical consequences. Furthermore, recent data suggest that the individual Framingham risk factors do not discriminate between a stable and unstable presentation (Figure 2).[3]

Clearly, novel risk markers are required that are based on an understanding of the biology of plaque destabilization, rupture, and thrombosis. A central concept is that of the "vulnerable plaque," which is defined as "a plaque that is at risk of becoming a future culprit lesion in an acute coronary syndrome or sudden cardiac death event." Figure 3 illustrates the classic features of a vulnerable plaque that have been demonstrated via pathologic and angiographic studies. A vulnerable plaque is characterized by a large lipid core that is separated from the vessel lumen only by a thin fibrous cap. The overall vessel area is increased by positive remodelling so that, despite a large amount of atheroma, minimal lumenal stenosis is evident.[4] Furthermore, there is increased T lymphocyte and macrophage activity within this vulnerable plaque. Disruption of the fibrous cap leads to superimposed thrombosis and vessel occlusion. In approximately 30% of culprit plaques, rupture is not seen and erosion of the superficial plaque surface is believed to precipitate thrombosis.

Inflammation and increased macrophage and T cell lymphocyte content are important features of vulnerable plaque. These inflammatory cells may act to thin the fibrous cap by producing proteolytic

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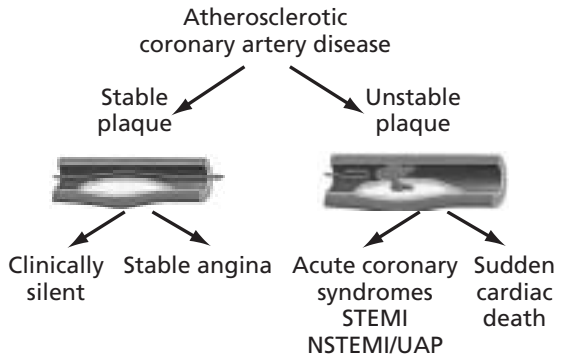
Figure 1: The manifestations of atherosclerotic CAD can be classified into those that arise from stable plaques and those that arise from unstable plaques.



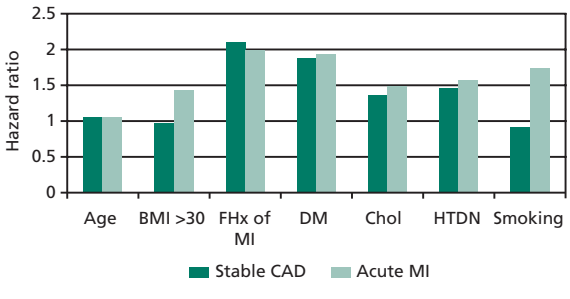
STEMI = ST elevation myocardial infarction
UAP = unstable angina pectoris

enzymes that degrade the plaque cap, reduce the amount of new fibrous material produced by smooth muscle cells, or cause smooth muscle cell apoptosis. Inflammation may be a systemic process, acting at multiple sites in the coronary tree. This possibility is highlighted by the finding of multiple disrupted plaques in some patients with acute coronary syndromes.[1]

Plaque ruptures may occur without producing acute coronary syndromes and are detected in patients with stable coronary disease and those dying from noncardiac causes. Disruption of the plaque surface exposes tissue factor and other highly thrombogenic contents in the underlying lesion. Although the determinants of outcome of a plaque rupture are not completely understood, the thrombosis system is believed to be of central importance.[5]

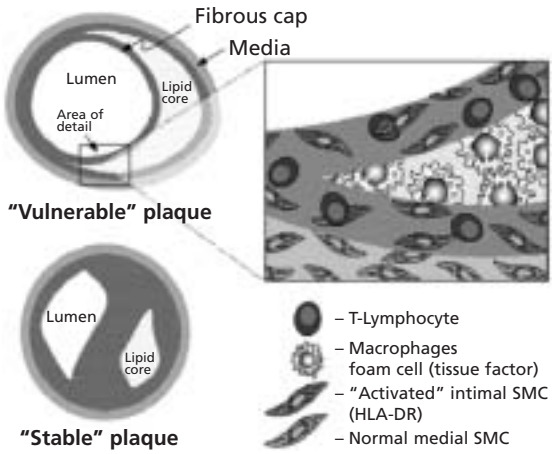
In recognition of the importance of both local plaque histology and systemic factors of inflammation and thrombosis, a panel of researchers has recently proposed that the concept of a vulnerable plaque alone should evolve to one that

Figure 2: Most of the risk factors in the Physicians Health Study provide little discrimination between stable CAD and acute MI except for BMI >30 and a history of smoking, which indicate that the first presentation of CAD will be acute, although only modestly.[3]



HTDN = hypertensive
FHx MI = family history of myocardial infarction
BMI = body mass index

Figure 3: A vulnerable plaque has a large lipid core separated from the vessel lumen by a thin fibrous cap. A stable plaque is generally composed of primarily fibrous tissue and a small lipid core that is far removed from the lumen.



SMC = smooth muscle cell

includes biomarkers and myocardium vulnerability and is integrated at the patient level.[6]

In vivo detection of vulnerable plaques

Most information about vulnerable plaques comes from pathologic studies. The prevalence and natural history of vulnerable plaque in patients is unknown and requires prospective study. Thus far, we have been limited by our inability to apply these diagnostic criteria in clinical situations. However, recent developments in invasive and noninvasive imaging have offered several promising approaches for vulnerable plaque detection.

Invasive plaque imaging

Intravascular ultrasound

Intravascular ultrasound (IVUS) is the most widely used intravascular imaging technique. However, the sensitivity of traditional IVUS in detecting lipid-rich plaque is limited. It was recently demonstrated that the raw radiofrequency data used to generate the IVUS grayscale image can be analyzed to achieve greater tissue characterization. The frequency distributions of these data have been shown to vary, based on the underlying tissue component. The accuracy of this approach is between 80% and 90%.[7] Sample images from patients with stable angina and acute coronary syndromes are shown in Figure 4.

An alternate approach to vulnerable plaque detection using IVUS is called elastography. This technique makes use of the conformational change in coronary vessels that occurs during the cardiac cycle. Increased pressure during systole causes distension of the vessel that is quantified as "strain." Regions with high strain are highly correlated with features of lipid-rich atheroma on histologic analysis.[8] Sensitivity and specificity for detection of vulnerable plaque is >90%. Figure 5 demonstrates a sample strain map with the corresponding grayscale IVUS

Figure 4: Sample images (in grayscale) using the virtual histology system. The stable lesion has mostly fibrous tissue with little lipid. The lesions in patients with unstable angina and acute MI have more extensive lipid-rich deposits adjacent to the lumenal surface.

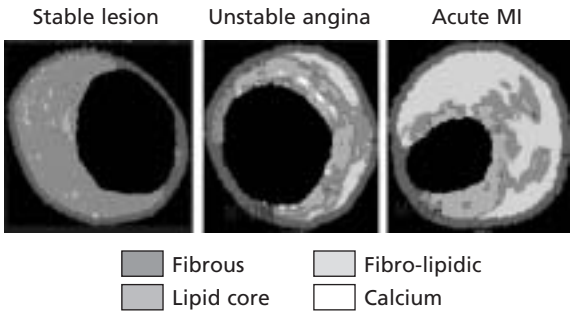


image. Note that the high strain (lightest) regions in the image on the right are seen at the shoulders of the plaque.

Other IVUS-based approaches incorporating microbubble contrast agents and targeted imaging methods are in development. The advantage of IVUS-based intravascular techniques is that they build on an imaging approach already in use and familiar to interventional cardiologists. In addition, imaging acquisition is rapid and can be performed over long segments of the coronary arteries and poses no additional risk to the patient.

Optical coherence tomography

Optical coherence tomography (OCT) is a new modality being developed for intracoronary imaging. It is analogous to IVUS, but uses infrared light waves instead of sound. Since the frequencies of infrared light are orders of magnitude higher than ultrasound signals, very high-resolution images that are up to 25 times greater than any existing modality can be

Figure 5: Local strain was calculated from the gated radiofrequency traces. The traditional IVUS image on the left demonstrates an eccentric plaque, that is relatively echo-poor and compatible with a lipid-rich plaque. The elastography image on the right reveals the highest strain (2%) in the lightest area; the 2 regions of increased strain are in the 12 o'clock and 5 o'clock positions, corresponding to the shoulder regions of the plaque.[8]

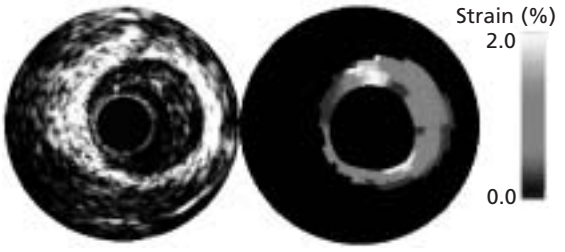
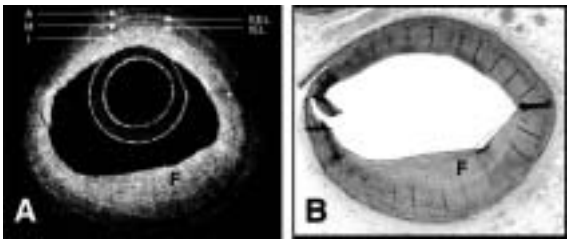


Figure 6: The sample OCT (A) shows ex vivo imaging of a coronary artery with visualization of the vessel lumen, catheter artifact, intima, media, and adventitia; the resolution is comparable to light microscopy (B).[9]



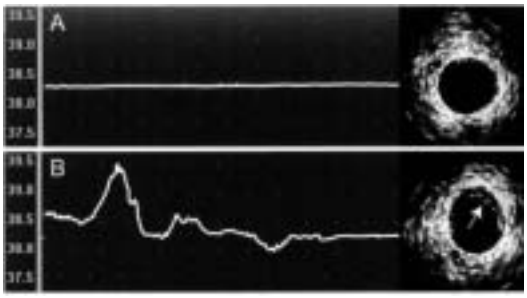
obtained. A sample image is shown in Figure 6 with a corresponding light microscopy image. The unparalleled anatomic detail of OCT allows for detailed characterization of plaque morphology and content. However, imaging requires a blood-free field, which limits imaging time and the length of the vessel that can be examined.[9]

Thermography

An alterative approach is to image functional aspects of plaque and provide an assessment of plaque activity. The prototype modality for functional plaque assessment is thermography. This technique uses a catheter-based thermistor to detect small temperature differences in regions of the coronary vessels. It is based on the hypothesis that superficial inflammation in vessels generates a higher surface temperature.[10]

Figure 7 shows a sample pull-back image from 2 patients, one with a normal vessel lacking thermal heterogeneity, and the second with marked thermal variation throughout the length of the plaque. Thermal heterogeneity is found in some patients with stable angina and in almost all patients with unstable angina, and 2 or even 3 hot plaques may be present in patients with an acute MI. Large clinical trials are underway to assess if temperature differentials are related to the site of

Figure 7: Two thermography images. The first patient (A) has little atherosclerotic disease and there is a lack of temperature hetereogeneity. The second (B), in a patient with disease, there is an area of increased temperature and significant temperature heterogeneity.[10]



vulnerable plaque. This technique may ultimately prove complementary to morphologic imaging for comprehensive lesion characterization.

Noninvasive plaque imaging

The ability to image coronary plaques noninvasively would be immensely valuable for a greater understanding of vulnerable plaques. In contrast to invasive techniques, noninvasive imaging could be performed with less patient risk, inconvenience, and cost. These assessments might then be performed more frequently and in intermediate-, as well as in high-risk patients, facilitating natural history studies and potentially, even monitoring systemic anti-atherosclerotic therapy. The two primary noninvasive techniques are computed tomography (CT) and magnetic resonance imaging (MRI).

Computed tomography

Multidetector CT (MDCT) has proven a robust technique for the detection of coronary calcification. Coronary calcium measurement by CT is predictive of future cardiac events, including MI and cardiac death. Calcium reflects atherosclerotic burden and the presence of advanced plaques that are responsible for events. However, location of calcium does not appear to correlate with vulnerable or ruptured plaques. In fact, unstable plaques may actually have reduced calcium.[11]

Techniques to directly image the coronary arteries with CT are rapidly being developed. CT coronary angiography performed with rapid, cardiac-specific imaging protocols and contrast administration can visualize the lumen of the coronary arteries as well as plaques in the vessel wall. Figure 8 shows recently published comparative MDCT and IVUS images. A low attenuation plaque is seen by CT that corresponds on cross-sectional display to the IVUS image.[12] Preliminary data suggest that CT may be able to classify plaque subtypes (eg, calcium-rich plaques have very high attenuation on CT [>120 Hounsfield units], while lipid-rich plaques have low density on CT [<50 Hounsfield units]).

Magnetic resonance imaging

MRI can identify the different components within an atherosclerotic plaque by use of multiple-pulse sequences such as T1, T2, and proton-density weighted. The appearance of each component of the plaque – such as lipid, fibrous tissue, hemorrhage and calcium – varies, depending on the pulse sequence used. For example, lipid will appear "high density" on T1 and proton density images, "intermediate" on time of flight images, and "variable" on T2 images. By using multiple pulse sequences, MRI can classify atherosclerotic plaque composition with high degrees of accuracy.[13] It is the preferred imaging technique for atherosclerotic plaque in the aorta and carotid.

Figure 8: Patient with noncalcified plaque in segments 6 and 7 of left anterior descending coronary artery (LAD).[12]
A: Axial MDCT image showing noncalcified plaque in segments 6 (proximal LAD; small arrows) and 7 (LAD distal to diagonal branch; larger arrow).
B: Multiplanar reconstructed MDCT image showing cross-section of LAD segment 7 with plaque (arrow). Arrowhead indicates diagonal branch.
C: IVUS image showing noncalcified plaque in segment 7 (arrows).
D - F: Patient with calcified and noncalcified plaque components in proximal LAD (segment 6). D: Axial MDCT image showing partly calcified plaque in proximal LAD (arrow).
E: Multiplanar reconstructed MDCT image showing cross-section of proximal LAD with plaque (large arrow) including calcification (small arrow). Arrowhead indicates contrast-enhanced lumen. F: IVUS image showing partly calcified plaque in proximal LAD (arrows).

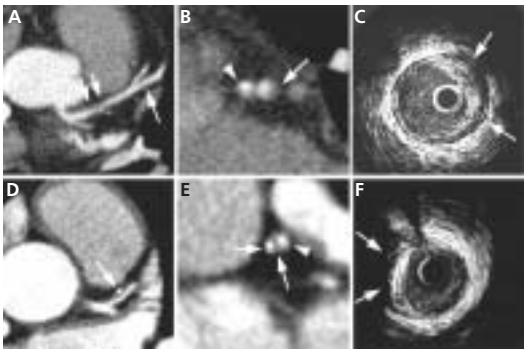


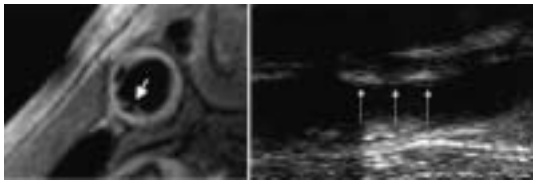
Figure 9 demonstrates an MRI of a carotid artery prior to endarterectomy. The fibrous cap is visualized and a break can be seen within it, exposing underlying lipid-rich atheroma.[14] For coronary applications, MRI is technically limited by problems of vessel motion. Compared to CT, an MRI produces much lower resolution images that require much longer scan times; for the most part, this technique is still under development.

Intense investigation over the past several years has now produced well-validated, imaging techniques, in particular, of intravascular images, for assessing vulnerable plaque. A number of ongoing studies are employing these techniques to examine plaque morphology prior to rupture and to assess the natural history of disease.

Biomarkers

The presence and activity of various biomarkers may be important in modifying the course of vulnerable plaques. Increased inflammatory and thrombotic activity may affect the propensity of a plaque to rupture and the

Figure 9: MRI can visualize rupture plaque and with molecular imaging may also detect thrombus.[14]



risk of subsequent thrombosis and vessel occlusion. Several inflammatory markers are under study, including C-reactive protein (CRP), interleukin 6, soluble CD40 ligand, and pregnancy-associated plasma protein A. All of these markers are elevated in patients with acute syndromes and are predictive of subsequent outcome.

Markers such as platelet polymorphisms, increased circulating tissue factor, fibrinogen, and plasminogen activator inhibitor 1 are potential novel markers of hypercoagulability. Other markers of a prothrombotic state such as antithrombin III deficiency, protein C or S deficiency, and resistance to activated protein C may be important. In addition, transient shifts in the coagulation and inflammatory activity and dynamic interactions between these systems are known to occur and may be important in contributing to acute events.[15]

Integrated risk stratification

The relative importance of anatomic, functional, or biomarker variables in predicting the outcome of vulnerable plaques is unknown. The ideal risk stratification approach will likely be multifactorial. In a recent review in *Circulation*, a pyramid outline was used to show how currently available tools might be implemented in the search for vulnerable plaques.[15]

- One would start by applying the Framingham risk score to identify patients at risk for atherosclerosis and instituting lifestyle interventions in that group.
- In a smaller subset with intermediate-risk features, assessment of systemic inflammatory activity and calcium score by CT plus potentially noninavsive angiography may help to further classify risk. These patients might benefit from initiation of a statin and acetylsalicyclic acid (ASA), plus other pharmacologic therapy for identifed risk factors.
- Finally, in the highest risk patients, invasive angiography with IVUS or another imaging technique would be performed to identify candidates for other invasive therapies.

The ultimate approach would have high predictive accuracy, safety, and cost-effectiveness. Future improvements in current screening techniques may be necessary to realize this goal.

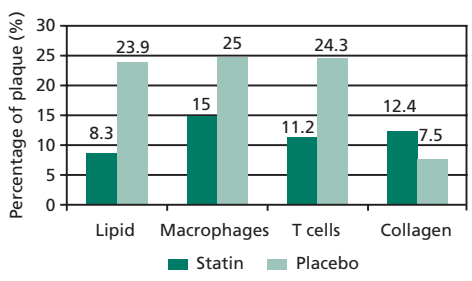
Therapeutic considerations

As we learn more about the diagnosis and natural history of vulnerable plaque, several questions are central in making decisions about the appropriate therapeutic approach. How many vulnerable plaques exist in a given patient? What is the time-course of vulnerability? What risk of adverse outcome can be assigned to each vulnerable plaque individually and to the patient as a whole? Answers to these questions will require natural history studies combining imaging and biomarker assessment. The central issue is whether identification of individual vulnerable plaques alters patient outcome. In general, two perpectives are held on the likely result.

One school of thought is that atherosclerosis is a diffuse disease and that vulnerable plaques are *multiple* in number. Given the low event rate in patients who have yet to have a cardiac event, the risk ascribed to individual plaques will inevitably be low. Therefore, the only conceivable approach to therapy will be systemic. Statins are a widely-used systemic therapy that substantially reduces the risk of future MI. It has been consistently demonstrated that the reduction in cardiac events with statins is not accompanied by a parallel reduction in the angiographic burden of disease. It is possible, therefore, that much of the improvement in outcome with statin use is from the stabilization of vulnerable plaque. This was suggested in a study in patients who were randomized to statin therapy or placebo in the 3 months prior to carotid endarterectomy. The composition of plaque extracted at surgery was analyzed and the results are shown in Figure 10. Note that after only 3 months of treatment, lipid, macrophage, and T-cell content was substantially reduced and plaque morphology shifted to a more stable form.[16]

An alternate viewpoint is that high-risk vulnerable plaques are *few* in number and that systemic therapy, though effective, may not be adequate to attenuate the

Figure 10: Trial of patients prior to planned endarterectomy comparing plaque composition after statin versus placebo therapy for 3 months. Statin therapy was associated with marked reductions in lipid and inflammatory cell content and increases in plaque collagen.[16]



risk associated with the most vulnerable lesions and direct local intervention may be required.

In fact, approaches to vulnerable plaques have become an important focus for interventional cardiology. If an effective interventional strategy can be found, percutaneous coronary intervention (PCI) may be able to overcome its prior inability to prevent future MI.[17] If local therapy is pursued, it will be important to establish if the risk of future adverse outcome of individual plaques justifies the upfront risk and cost of prophylactic intervention.

Conclusion

Recognition of the concept of vulnerable plaque is now widespread. Controversy remains about clinical diagnostic criteria, although several promising approaches are now available. These approaches have facilitated an understanding of the natural history of vulnerable plaque and lay the foundation for subsequent therapy trials. As the treatment of acute coronary occlusions and stable high-grade stenoses becomes increasingly effective, vulnerable plaque will represent an important frontier for cardiology. Identifying and treating vulnerable plaques may offer a substantial new avenue for improving the outcome of patients with coronary artery disease.

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