Intravascular Modalities for Detection of Vulnerable Plaque
Current Status

Briain MacNeill, Briain D. MacNeill, Harry C. Lowe, Masamichi Takano, Valentin Fuster, Ik-Kyung Jang

Abstract—Progress in the diagnosis, treatment, and prevention of atherosclerotic coronary artery disease is dependent on a greater understanding of the mechanisms of coronary plaque progression. Autopsy studies have characterized a subgroup of high-risk, or vulnerable, plaques that result in acute coronary syndromes or sudden cardiac death. These angiographically modest plaques share certain pathologic characteristics: a thin, fibrous cap, lipid-rich core, and macrophage activity. Diagnostic techniques for vulnerable-plaque detection, including serologic markers and noninvasive and invasive techniques, are needed. Recent advances in intravascular imaging have significantly improved the ability to detect high-risk, or vulnerable, plaque in vivo by using various features of plaque vulnerability as methods of identification. The characteristic anatomy of a thin, fibrous cap overlying a lipid pool has promoted high-resolution imaging, such as intravascular ultrasound, optical coherence tomography, and intracoronary magnetic resonance. The lipid-rich core is identifiable by angioscopically detected color changes on the plaque surface or by its unique absorption of energy, or “Raman shift,” of its cholesterol core, driving coronary spectroscopy. Finally, temperature heterogeneity arising at foci of plaque inflammation has prompted the development of intracoronary thermography. In this review, we will discuss these techniques, their relative advantages and limitations, and their potential clinical application. (Arterioscler Thromb Vasc Biol. 2003;23:650–666.)

Please provide 3–5 key words

Atherosclerosis and its thrombotic complications are the leading cause of morbidity and mortality in industrialized countries. Progress in the diagnosis, treatment, and prevention is dependent on a greater understanding of the mechanisms of atherosclerotic plaque progression. Lack of a suitable large-animal model for atherosclerotic plaque rupture has concentrated research efforts on pathologic studies and imaging modalities to advance our understanding of the pathogenesis of vulnerable plaque.

Historically, revascularization techniques of coronary artery bypass surgery and percutaneous coronary intervention (PCI) have targeted flow-limiting, hemodynamically significant stenoses, which are readily detected by coronary angiography. However, it is now accepted that acute coronary syndromes most commonly result from disruption of atherosclerotic plaques that are angiographically modest in severity.1–3 This concept is echoed in studies of plaque regression syndromes most commonly result from disruption of atherosclerotic plaques that are angiographically modest in severity.1–3 This concept is echoed in studies of plaque regression syndromes most commonly result from disruption of atherosclerotic plaques that are angiographically modest in severity.1–3 This concept is echoed in studies of plaque regression syndromes most commonly result from disruption of atherosclerotic plaques that are angiographically modest in severity.1–3 This concept is echoed in studies of plaque regression syndromes most commonly result from disruption of atherosclerotic plaques that are angiographically modest in severity.1–3 This concept is echoed in studies of plaque regression syndromes most commonly result from disruption of atherosclerotic plaques that are angiographically modest in severity.1–3 This concept is echoed in studies of plaque regression syndromes most commonly result from disruption of atherosclerotic plaques that are angiographically modest in severity.1–3 This concept is echoed in studies of plaque regression syndromes most commonly result from disruption of atherosclerotic plaques that are angiographically modest in severity.1–3 This concept is echoed in studies of plaque regression syndromes most commonly result from disruption of atherosclerotic plaques that are angiographically modest in severity.1–3 This concept is echoed in studies of plaque regression syndromes most commonly result from disruption of atherosclerotic plaques that are angiographically modest in severity.1–3 This concept is echoed in studies of plaque regression syndromes most commonly result from disruption of atherosclerotic plaques that are angiographically modest in severity.1–3 This concept is echoed in studies of plaque regression syndromes most commonly result from disruption of atherosclerotic plaques that are angiographically modest in severity.1–3 This concept is echoed in studies of plaque regression syndromes most commonly result from disruption of atherosclerotic plaques that are angiographically modest in severity.1–3 This concept is echoed in studies of plaque regression syndromes most commonly result from disruption of atherosclerotic plaques that are angiographically modest in severity.1–3 This concept is echoed in studies of plaque regression syndromes most commonly result from disruption of atherosclerotic plaques that are angiographically modest in severity.1–3 This concept is echoed in studies of plaque regression syndromes most commonly result from disruption of atherosclerotic plaques that are angiographically modest in severity.1–3 This concept is echoed in studies of plaque regression syndromes most commonly result from disruption of atherosclerotic plaques that are angiographically modest in severity.1–3 This concept is echoed in studies of plaque regression syndrome.

In recent years, cardiovascular research has sought potential strategies for detecting high-risk plaques before their disruption. These potentially powerful techniques are aimed at identification of populations at risk and plaque monitoring and might eventually guide targeted therapy. Proposed diagnostic tools include serologic techniques and noninvasive and invasive imaging. This review focuses on invasive modalities, summarizes the recently developed invasive techniques, and compares their advantages and limitations.

Definition of Vulnerable Plaque
Although progression of atheromatous plaque has been well described and atherosclerotic lesion types characterized, the concept of the vulnerable plaque is a novel one.1,2 The term “vulnerable plaque” refers to a subgroup of often modestly stenotic plaques that are prone to rupture or erosion, often resulting in acute coronary syndromes and sudden cardiac death.3 Postmortem evaluation has shown that rupture-prone plaques have certain characteristics: a thin, fibrous cap (<65 μm); a large, lipid-rich pool; and increased macrophage activity (Figure 1).4–8 Cellular mechanisms thought to predispose to plaque vulnerability include reduced collagen synthesis, local overexpression of collagenase, and smooth muscle cell apoptosis.4 These molecular changes appear most prominent at the plaque shoulder, where mechanical strain is
maximized.\textsuperscript{9,10} It has been suggested that disruption in cap integrity releases procoagulant factors, particularly tissue factor, creating a nidus for thrombus formation and the potential for an acute coronary event.\textsuperscript{11} Although vulnerable plaques continuously rupture throughout the vasculature, only certain plaques form an occlusive thrombus, causing clinical syndromes.\textsuperscript{12} Factors that determine the fate of a plaque rupture are unknown.

The terms “vulnerable plaque” and “high-risk plaque” are imperfect, in that they are predictive, prophetic, or prospective in nature. A more descriptive term, such as “thin-capped fibroatheroma,” is often favored; however, for the purpose of this review, these terms will be used synonymously.

**Invasive Imaging Techniques**

Coronary plaque begins eccentrically and induces a process of remodeling, resulting in arterial dilatation and preservation of the luminal area.\textsuperscript{2,13,14} Coronary angiography, historically the “gold standard,” illustrates luminal narrowing but does not provide direct information on the changes within the vessel wall necessary to detect vulnerable plaque.\textsuperscript{2} This limitation has promoted interest in alternative invasive or catheter-based techniques to directly visualize the arterial wall and to characterize plaque composition. Invasive techniques are, by definition, associated with procedural risk, limited to a specific region of the coronary arterial tree, and inappropriate for screening large populations.

Various plaque components have been targeted to determine potential vulnerability of individual plaques (Table 1). The characteristic architecture of a thin, fibrous cap overlying a lipid pool has prompted further development of high-resolution imaging modalities, including intravascular ultrasound (IVUS), optical coherence tomography (OCT), and intracoronary magnetic resonance. The cholesterol-rich, lipid core underlying the fibrous cap is also identifiable by both angioscopically detected color changes reflected on the plaque surface and its unique absorption of energy, or “Raman shift,” of its cholesterol crystals, thus driving the development of coronary spectroscopy. Finally, temperature heterogeneity arising at foci of plaque inflammation has promoted the development of intracoronary thermography.

**Figure 1.** Histology of a lipid-rich, or vulnerable, coronary plaque. The thin fibrous cap (arrows) and lipid core (LC) are features of vulnerable coronary plaque. Of note, the preserved luminal area renders coronary angiography or other forms of laminography obsolete in vulnerable-plaque detection.

<table>
<thead>
<tr>
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<td>IVUS</td>
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<td>Intravascular MRI</td>
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NA indicates not applicable; CS, clinical studies; CA, clinically approved for commercial use; CA*, clinically approved commercial use in Japan; PCS, preclinical studies; UK, unknown.

\(+++\)=sensitivity >90%; \(++\)=sensitivity 80% to 90%; \(+\)=sensitivity 50% to 80%; [en]=sensitivity <50%.
Intravascular Ultrasound

IVUS has provided insight into the extent and distribution of atherosclerotic plaque, allowing characterization of vessel wall and plaque morphology. IVUS is capable of characterizing the plaque core, although with less sensitivity for lipid-rich than calcified lesions. Plaque morphology can be described by ultrasound as echoreflective, corresponding to calcified plaque; hyperechoic, representing fibrous plaque; and hypoechoic, indicating a lipid-rich core. Plaque characterization is reliable in distinguishing fibrous and calcified plaque but not soft or lipid-rich plaque, owing in part to variable concentrations of cholesterol crystals and calciospheres that form the heterogeneous components of the cholesterol core. In terms of macrocalcification, IVUS yields a 3-fold higher detection rate compared with angiography, with a sensitivity and specificity of 89% and 97%, respectively. However, the echo-reflective properties of calcium result in acoustic shadows that preclude accurate quantification and obscure imaging of adjacent structures. With regard to the IVUS detection of microcalcification, defined as flecks of calcium <0.05 mm, a sensitivity as low as 17% was found. The importance of calcium in plaque vulnerability remains an issue of ongoing debate.

The 2-dimensional IVUS image, derived from ultrasound frequencies in the range of 20 to 40 MHz, results in an axial resolution of 100 to 200 μm and a lateral resolution of 250 μm. These properties, though beneficial for visualizing deep structures, limit imaging of microstructure, yielding a sensitivity of only 37% for the detection of plaque rupture with IVUS. Although 3-dimensional image reconstruction improves border definition, it has not yet been tested for detection of vulnerable plaque or plaque disruption.

Several techniques have been developed to improve the IVUS detection of plaque vulnerability. To maximize the differentiation of a lipid-rich or sonoluent plaque, integrated backscatter (IB) and assessment of the radiofrequency envelope within the plaque have been analyzed. Correlation of the parameters of the radiofrequency envelope generated from ex vivo plaque with histologic markers of plaque vulnerability have yielded modified algorithms that augment the detection of the lipid-rich core associated with plaque vulnerability. In vivo application of IB IVUS has recently been shown to enhance visualization of plaque characteristics and improve the resolution to ~40 μm. Two important limitations of IB IVUS include the analogous signal obtained from intimal hyperplasia and lipid-rich plaque, necessitating complex methodology for adequate differentiation, and second, a significant reduction in the sensitivity of plaque characterization as imaging moves off axis.

The intracoronary pressure changes of the cardiac cycle exert forces resulting in conformational change in coronary plaque that have been proposed as predictors of plaque vulnerability. IVUS elastography combines ultrasound images with radiofrequency measurements to detect regions of increased strain that are prone to rupture, thus improving the discrimination between lipid-rich and fibrous plaque, traditionally a limitation of standard IVUS. Furthermore, ex vivo IVUS elastography has demonstrated a positive correlation between strain measurements and the presence of macrophages and an inverse relation with the quantity of smooth muscle cells within coronary plaque, supporting the role of macrophage-derived matrix metalloproteinases in the development of thin-capped, vulnerable plaque. Recently, an in vivo animal study validated IVUS elastographic criteria for identifying lipid-rich plaque and demonstrated a sensitivity and specificity of 92% in identifying the presence of macrophages at foci of increased strain within the plaque. Although beneficial in segregating plaque types, IVUS elastography has been criticized for its inability to differentiate normal artery from early and advanced fibrous plaques.

Related structural properties that have been studied as markers of vulnerability include plaque distensibility and remodeling. Plaque disruption is ultimately triggered by intrinsic changes and/or extrinsic forces, including shear stress and wall stress. Plaque distensibility provides a measure of wall stiffness, a marker of the dynamics of intrinsic changes and extrinsic forces, and has been related to plaque distribution and thickness. Distensibility, calculated with gated IVUS images and intracoronary pressures, is correlated with the angioscopic categorization of vulnerable plaque and OCT features of lipid-rich plaque (Figure 2). Distensibility measurements can, however, be confounded by axial motion of the IVUS catheter during the cardiac cycle, resulting in systolic and diastolic images of different sites.

Observations of focal arterial dilatation at the site of aortic and coronary plaque have led to theories of arterial remodeling in response to plaque development. Coronary luminal area was shown to be preserved during early plaque progression owing to a process of internal elastic lamina dilatation, termed “positive remodeling.” Similarly, “negative remodeling” describes shrinkage of the external elastic membrane in response to plaque development. Although initially thought of as a protective or beneficial process in reducing effective percent stenosis, positive remodeling has been associated with acute coronary syndromes and angioscopically complex lesions. Negative remodeling, on the other hand, is seen more frequently in stable coronary artery disease. The pathophysiology of vascular remodeling and the mechanisms that link plaque vulnerability to remodeling are unclear. Hemodynamic and humoral effects are thought to result in secretion of factors that influence cell proliferation, apoptosis, and the composition of extracellular matrix. Histologic studies of remodeled arteries demonstrate an inflammatory process similar to that seen in vulnerable plaque. Limited clinical studies have shown positive remodeling associated with high lipid levels and negative remodeling associated with lipid-lowering therapy, suggesting that remodeling is significant in plaque vulnerability and stabilization.

Potential artifacts that arise with IVUS include “ring-down” artifacts produced by acoustic oscillations in the piezoelectric transducer that obscure near-field images and “nonuniform rotational distortion,” arising from uneven drag on the cable, causing cyclic oscillations of the ultrasound probe. Specific limitations to the IVUS identification of vulnerable plaque remain the issues of resolution and inability to adequately discriminate between fibrous and lipid-rich plaques. The combination of new, high-frequency catheters...
integrated with the techniques of IVUS signal modification will certainly enhance the role of IVUS in vulnerable-plaque detection. Balancing these limitations is the significant experience that exists in the clinical application and interpretation of this modality and the capability to image long arterial segments safely.

**Angioscopy**

Although historically attempts have been made to visualize intracardiac structures, it was not until the development and application of fiberoptics that direct visualization of coronary arteries could be achieved. Coronary angioscopy complements angiography by characterizing plaque composition and illuminating the presence of thrombus or endoluminal irregularities, such as ulcerations, fissures, or tears.

The normal artery appears angioscopically as glistening white, whereas atherosclerotic plaque can be categorized on the basis of its angioscopic color as yellow or white (Figure 3). Histologic correlation has demonstrated high concentrations of cholesterol-laden crystals seen through a thin, fibrous cap in yellow plaque and a thick, fibrous cap in smooth white plaques. Platelet-rich thrombus at the site of plaque rupture is characterized as white granular material, and fibrin/erythrocyte-rich thrombus, as an irregular, red structure protruding into the lumen. Furthermore, yellow plaques are seen more commonly at the site of culprit lesions, increase the likelihood of a subsequent coronary event, and demonstrate increased susceptibility to rupture and thrombosis with increased intensity of yellow color, all supporting the concept that yellow lesions correspond to vulnerable plaque.

Both culprit and nonculprit, infarct-related, vulnerable, yellow plaques followed up angioscopically for 6 months have demonstrated a significant reduction in maximum intensity of yellow color and associated thrombus, albeit less completely in diabetes and hyperlipidemia. Changes in plaque color have also been recorded with lipid-lowering interventions.

Rupture of vulnerable, yellow plaque has also been demonstrated in asymptomatic stable angina, in which the prevalence of “silent” plaque rupture diagnosed angioscopically was 29.3% and was significantly more prevalent in diabetes and hypertension. Furthermore, the presence of yellow plaque at the time of PCI has been shown to be an independent risk for future ischemic events in a prospective, 5-year angioscopic study. The mechanical features of vulnerable plaque have been studied with a combination of angioscopy and IVUS in which yellow and white plaques were compared in terms of stiffness, distensibility, and remodeling. Yellow plaques demonstrated increased distensibility and compensatory remodeling, thought to predispose to mechanical fatigue from repetitive strain at the shoulder regions of coronary plaque.

The most significant limitation of current angioscopic systems is the need to create a blood-free field. This is achieved with a proximal occluding balloon, which itself can create complications, the most devastating of which include coronary rupture, dissection, thrombosis, or arrhythmia. The alternative system uses a smaller catheter to continuously flush saline in front of the angioscope to transiently displace blood, but this technique requires removal of the guidewire before acquisition of each image. The catheter design (3.0 to 5.0F) of both systems precludes angioscopic evaluation of small vessels (<2 mm) and renders assessment of cross-stenotic lesions difficult (please see http://www.ahajournals.org). Moreover, the subjectivity of color interpretation has been criticized, resulting in efforts to develop an automated analysis system of angioscopic images. Finally, angioscopy images only the luminal surface, and although changes in the vessel wall are reflected on the surface, this might not be sufficiently sensitive to detect subtle alterations in plaque.

**Figure 2.** Stationary IVUS images during diastole (A) and systole (B) demonstrate the distensibility of coronary plaque during the cardiac cycle, which can be quantified by the distensibility index. Vulnerable plaques, identified by angioscopy, have been shown to display greater distensibility. Tick marks=0.5 mm
composition, a feature that has been raised in recent comparisons of imaging modalities.\textsuperscript{25}

**Optical Coherence Tomography**

OCT measures backscattered light, or optical echoes, derived from an infrared light source directed at the arterial wall, and as such, it can be regarded as an analogue of IVUS.\textsuperscript{52} Resolution capabilities of 2 to 10 μm, validated ex vivo, allow superior definition of the order necessary to resolve thin, fibrous caps that are responsible for plaque vulnerability, whereas the heterogeneous morphologies of coronary plaque are readily discernible into calcified, fibrous, and lipid

**Figure 3.** Angioscopic color grading of atherosclerotic coronary plaque, with white plaque representing fibrous plaque (A). Yellow plaque signifies a lipid-rich core seen through a thin, fibrous cap. The intensity of the image increases as the fibrous cap thins and becomes increasingly transparent (B, C, and D). An irregular or complex lipid-rich plaque is shown in E, and a lipid-rich plaque with associated thrombus is shown in F. A 0.014-in. wire in D provides a reference of scale.

**Figure 4.** In vivo intracoronary imaging of lipid-rich plaque with OCT (A) and IVUS (B). The OCT image demonstrates the superiority of resolution, whereas the IVUS image highlights greater image penetration. A thin, fibrous cap, marked with an arrow, is seen to overlie a lipid-rich core (LC). GW indicates guidewire artifact.
rich (Figure 4).\textsuperscript{53,54} OCT characteristics of various plaque components have been established by ex vivo histologic correlation, highlighting a sensitivity and specificity of 92\% and 94\%, respectively, for lipid-rich plaque; 95\% and 100\% for fibrocalcific plaque; and 87\% and 97\% for fibrous plaque.\textsuperscript{55}

In a comparison with high-resolution IVUS, OCT has proved equivalent in detecting plaque and discerning fibrous and calcified plaque morphologies. In terms of resolution, OCT was found to be superior, allowing identification of intimal hyperplasia, internal and external elastic lamina, and regions of lipid-rich plaque not detected by IVUS.\textsuperscript{53} Importantly, this study demonstrated the clinical application of OCT and its superiority to IVUS in detecting characteristics of vulnerable plaque.\textsuperscript{53} Recently, the ability of OCT to detect and quantify macrophage infiltration was demonstrated in an autopsy study. The presence of macrophages within the fibrous cap, identified by immunoperoxidase staining for CD68, was correlated with the optical signal, such that a sensitivity and specificity of 100\% was achieved for the detection of an arbitrary quantity of 10\% CD68-positive macrophages within that imaged region.\textsuperscript{56}

Newer platforms that are being applied to coronary OCT include polarization imaging, spectroscopy, Doppler, and elastography. OCT is extremely sensitive to changes in light polarization; the major source of polarization contrast, or birefringence, originates from fibrous plaque or cholesterol crystals, thus potentially advancing plaque discrimination. The addition of spectroscopic analysis supplements the structural detail of OCT with biochemical analysis of the plaque core, providing synergism in plaque imaging. OCT elastography, as with its IVUS counterpart, applies high-resolution imaging with radiofrequency measurements to detect foci of increased strain that are prone to plaque rupture. New wire-based systems with a diameter of 0.014 in. facilitate imaging of the smallest coronary arteries.

Current limitations of OCT remain significant and are related predominantly to the features of a light-based energy source, including poor tissue penetration and interference from blood. The latter necessitates techniques similar to angioscopy that displace blood, such as saline injection with or without a proximal occlusion balloon. These maneuvers limit prolonged image acquisition and preclude screening long arterial segments. A penetration of 2 mm, though considerably less than that with IVUS, is probably sufficient to detect the features of plaque vulnerability that are predominantly superficial in location.

**Thermography**

In union with the structural changes described earlier are the biologic processes that characterize the pathophysiology of vulnerable plaque. One such process is an intense inflammatory reaction, manifested by the local invasion of macrophages and lymphocytes, and the deposition of matrix metalloproteinases that degrade the supporting collagen and promote plaque fragility.\textsuperscript{2} This inflammatory activity creates local elevations in temperature that can be detected with a catheter-based thermistor with a temperature differentiation of 0.05°C and a spatial resolution of 0.5 mm.\textsuperscript{57,58} Ex vivo carotid plaque has demonstrated temperature heterogeneity directly proportional to the degree of histologically detected inflammation, confirming its ability to quantify the pathophysiologic process within plaque.\textsuperscript{57} Clinically, coronary arterial temperature differentials are greater in patients who present with acute coronary events and are associated with a higher adverse event rate after successful PCI, both suggesting a predictive role for thermography.\textsuperscript{59,60} Similarly, cell adhesion molecules, which mark the inflammatory process central to the pathogenesis of coronary artery disease, have been correlated with temperature differentials at culprit lesions in acute coronary syndromes.\textsuperscript{61} Finally, plaque stabilization with lipid-lowering therapy reportedly reduces temperature heterogeneity, supporting an anti-inflammatory effect of statin therapy.\textsuperscript{58}

There appears to be a significant overlap between temperature differentials in stable and unstable presentations of coronary artery disease, and there is no clear evidence that temperature differentials are related to a specific plaque vulnerability rather than a generalized marker of inflammation, in which case, a serologic marker might be more appropriate.\textsuperscript{58–62} Similarly, individual variations in temperature heterogeneity have been documented, suggested to arise from altered blood flow through a stenotic lesion or as a result of systemic inflammation or medication, all features that question its capacity to assess individual plaque vulnerability.\textsuperscript{58} Although several catheter designs are currently available, all require contact with the arterial wall, and their use can therefore be complicated by vessel injury (please see <http://www.ahajournals.org>). Without the structural definition obtained from high-resolution imaging modalities, the independent role of thermography seems limited. Furthermore, the immediate evaluation of local mechanical therapy and the selection of an appropriate site for background measurement are confounded.\textsuperscript{58} However, combining thermography with the structural detail of other imaging modalities theoretically produces an attractive synergy of anatomic and physiologic predictors of plaque vulnerability.

**Spectroscopy**

Spectroscopy, the study of energy wavelengths, has been investigated as a method of detecting vulnerable plaque by using different energy sources, including infrared or laser.\textsuperscript{63–65} To date, the most validated methods are Raman spectroscopy (RS) and near-infrared spectroscopy (NIRS). Raman spectra are created by processing the collected light scattered from an artery that is emitted during laser illumination. The Raman spectrum of a given molecule is unique, allowing analysis of chemical composition from the patterns of reflected light, known as diffuse reflectance spectroscopy. The molecular characteristics of lipid and calcium salts render RS highly sensitive for plaque detection, as demonstrated both in vivo and in vitro.\textsuperscript{53,66} By combining the independent spectra of the various chemical constituents of atherosclerotic plaque, a diagnostic algorithm has been validated to classify coronary artery plaques with a specificity of 94\%.\textsuperscript{67}

Combining IVUS and RS in an ex vivo study demonstrated synergism between the structural definition of IVUS and the
chemical quantification of RS, in which spectroscopy accurately identified and quantified calcium salts and cholesterol.\textsuperscript{66} Limitations of RS lie in the small number of photons recruited into the Raman shift, resulting in poor tissue penetration, low signal-to-noise ratio, and background noise from backscattered light within the optical fibers of the catheter-based system.

NIRS measures diffuse reflectance signals by using infrared light as an energy source. Infrared light results in greater tissue penetration than RS (2 mm compared with 0.3 mm) but a lower capability to identify individual components of plaque, resolved in part by the use of pattern recognition for plaque typing. Quantification of cholesterol within atherosclerotic plaque by NIRS correlates well with more destructive, traditional techniques of chromatography (correlation coefficient=0.926) in aortic plaque.\textsuperscript{68} Vulnerable plaque is thought to emit a unique spectrum, in part because of its lipid core and thin fibrous plaque but also as a result of physiologic variables such as pH.\textsuperscript{69} In human atherosclerotic plaque, NIRS achieved a sensitivity of 90% and a specificity of 93% for detection of the lipid core.\textsuperscript{64} The sensitivity and specificity for features of plaque vulnerability ranged from 77% to 93% for the fibrous cap and inflammation.\textsuperscript{64} It remains unclear whether combining the predictive value of each component might result in an even greater sensitivity and specificity for vulnerable-plaque detection. Incorporating measurements of temperature and pH into the spectroscopic system has been proposed to further improve high-risk-plaque detection.\textsuperscript{70}

Transferring ex vivo spectroscopy to in vivo coronary imaging raises several hurdles, not the least of which is noncontact spectroscopic evaluation through flowing blood, although in theory and initial practice, this seems feasible.\textsuperscript{64,71} As with thermography, lack of structural definition hinders all methods of spectroscopy, limiting their independent application in vulnerable-plaque detection, however combined with an imaging technique such as IVUS, OCT, or angiography, it might provide a valuable additional dimension.

Intravascular Magnetic Resonance Imaging

In superficial large arteries such as the carotid, standard magnetic resonance imaging (MRI) is capable of discriminating plaque components, including lipid, collagen, thrombus, and calcium on the basis of biochemical properties.\textsuperscript{72} As the distance from the external coil and the artery increases, however, a significant fall-off in signal to noise occurs, resulting in reduced resolution. A practical solution to improve imaging in deeper arteries is to insert intravascular coils in the artery or the adjacent vein.\textsuperscript{73} Several intravascular coil designs have been developed, each demonstrating superior resolution than standard MRI for vessel wall imaging (160 \(\mu\)m compared with 300 \(\mu\)m). Ex vivo aortic imaging with a 5F intravascular MRI probe and a 1.5-T scanner yielded sufficient resolution to discern the adventitial, medial, and intimal layers and to allow plaque characterization with a sensitivity of 83% and 100% for detection of fibrous cap and necrotic core, respectively.\textsuperscript{74} Furthermore, basic grading of plaque characteristics as mild, moderate, or severe displayed a correlation between histology and intravascular MRI of 75% and 74% for cap thickness and extent of necrotic core, respectively.\textsuperscript{74} With use of a standard 0.5-T MRI combined with a 5F intravascular MRI coil, the signal properties of fibrous cap, lipid core, calcium, thrombus, and edema were characterized within carotid plaque, demonstrating that through a variety of imaging approaches, standard magnets could achieve a sufficient degree of resolution, thus expanding their availability (Figure 5).\textsuperscript{75} In this study, in which a variety of imaging protocols were assessed, the discrimination between T1- and T2-weighted images proved time consuming and less informative than the use of various pulse sequences (inversion recovery, magnetization transfer contrast, and gradient echo sequences) that capitalized on the differences in biochemical composition of various plaque components.\textsuperscript{75} Limited in vivo studies suggest that intravenous MRI is effective through flowing blood, although the applicability of plaque characterization validated ex vivo remains unknown.\textsuperscript{76}

Current intravascular MRI coil designs are hampered, to varying degrees, by common themes that limit their clinical application. Catheters are typically 5F in outer diameter and require a close match between coil and arterial diameter to prevent fall-off in radial resolution. Furthermore, axial resolution is limited, necessitating multiple catheter manipulations and repeated imaging. Finally, image quality is reduced significantly as the intravascular coil moves off axis from the external magnet field, a significant limitation for imaging tortuous coronary arteries. Despite these considerable difficulties, the image quality and the recent development of MRI-compatible catheters make intravascular MRI an area of intense research.

Emerging Technologies

Several new developments, including pharmacologic and mechanical interventions, might augment vulnerable-plaque detection in the future. Such pharmacologic interventions target specific receptor activation, cell metabolism, or biologic pathways to enable a holistic evaluation by marrying structural morphology with biologic activity. Although nuclear imaging has achieved many of these goals, including receptor activation, metabolism, and apoptosis, the image resolution is limited by the distance from the tracer to the detector.\textsuperscript{77–79} Improvements in signal-to-noise ratio have been achieved with the application of intravascular catheter-mounted detectors, allowing enhanced sensitivity for detecting changes within atherosclerotic plaque (please see \textless http://www.ahajournals.org\textgreater).\textsuperscript{80} Recently, metal nanoparticles have been explored as contrast agents to enhance various imaging techniques.\textsuperscript{81} The nanoparticle’s ability to enhance both linear and nonlinear optical processes at low energy result in high resonant scattering to which optical imaging is particularly sensitive.\textsuperscript{82} Their high biocompatibility and small diameter (5 to 10 \(\mu\)m) allow easy diffusion through cellular junctions and phagocytosis by macrophages, enhancing detection of inflammatory processes. Newer generations of molecular probes demonstrate enzyme-specific fluorescence that is detectable by diffuse optical or fluorescence-mediated tomography.\textsuperscript{83} These probes are quenched in the inactive state but fluoresce brightly when activated on cleavage by specifically targeted enzymes. In a similar manner, quantum dots or nanocrystals,
which emit photonic energy, can be tagged with specific antibodies to function as cellular beacons that are visible to optical modalities.84

Interest in the development of microelectromechanical systems (MEMS) for medical applications has exploded in recent years. In the most general sense, this technology attempts to exploit and extend the fabrication techniques used in the microelectronics industry to medicine. The most immediate potential of MEMS in intravascular imaging includes the development of smaller catheter systems with a higher sensitivity and signal amplification. MEMS will also facilitate the development of multimodality sensors to combine the discriminatory power of 2 or more modalities to resolve the remaining challenges within invasive imaging.

**Application of Novel Technologies**

The value of any diagnostic procedure is dependent on the availability of effective treatment options. Concerning vulnerable plaque, the arsenal of potential therapies is sadly lacking. Plaque stabilization holds promise but is only partially effective, evidenced by the 50% to 70% of acute coronary events that it fails to prevent.85 Other pharmacologic solutions have been suggested and await further studies.85

In the era of drug-eluting stents, local mechanical treatment might hold promise, including local genetic or photodynamic therapies for plaque stabilization. The development of these novel imaging modalities opens new avenues of research that will likely define the future treatment of vulnerable plaque. The relative merits of invasive, noninvasive, and serologic markers will ultimately be decided on the basis of the optimum treatment strategies. If plaque stabilization remains the domain of pharmacologic therapy, then risk factor assessment in union with a serologic marker is sufficient to determine treatment. If, however, localized or targeted intraarterial therapy proves successful, then the need for structural definition and precise localization will drive imaging modalities.

Beyond research, however, do these novel technologies serve a role within current clinical practice, and if so how, will they be optimally employed? The answer is unknown and is likely to remain so until natural history studies are complete for clarification of the determinants of plaque vulnerability and specifically, the features that result in symptomatic plaque rupture. One can speculate that these novel tools are best adopted as a continuum of currently available diagnostic tools in which high-risk populations would be identified through application of currently recommended risk factor assessment, in addition to inflammatory markers or genetic analysis.86 In addition to instigating aggressive risk factor modification, a proportion of these

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Figure 5. Intravascular MRI of a carotid artery with corresponding histology (A) demonstrates a modestly elevated signal intensity in lower half of a T1 sequence. B, The same region during water signal suppression in the inversion recovery sequence, demonstrating persistent signal in the lower half of the artery, thus differentiating this region as high in lipid content and improving the differentiation of lipid plaque from the external fibrous intima in the upper half of the image. C, Corresponding hematoxylin-and-eosin-stained slide with high magnification of the selected region, confirming the presence of lipids and cholesterol crystals. D, Trichrome stained slide, with high magnification of the selected region displayed in F illustrates the fibrous cap above lipid pool that is seen in the intravascular MRI (B).75
patients might warrant further evaluation, in which, for instance, a noninvasive imaging modality might provide a better risk assessment and highlight regions within the arterial tree that were of particular concern.97–99 Targeted intravascular imaging at these sites would definitively characterize the plaque site and ideally provide a measure of the risk of plaque disruption. Such a vulnerability index would allow a clear decision analysis toward appropriate therapy.

The optimum modality for intravascular imaging remains undefined. Each modality possesses unique advantages that might be synergistic. For example, combination of a high-resolution imaging modality with a biologic measurement from spectroscopy or thermography augments structural detail with functional assessment of metabolic or molecular changes. Similarly, with OCT and IVUS, the potential for synergism exists, as their relative advantages and limitations are complementary: OCT provides high resolution but poor penetration, whereas IVUS yields superior penetration but poor resolution.

Conclusions

Greater understanding of the biology of atherothrombotic disease drives interest in detection of vulnerable plaque. The ability to detect and monitor vulnerable plaque is keenly sought to define its natural history and support studies of progression and regression. A number of novel imaging modalities have recently been proposed to identify specific areas of plaque vulnerability. Defining the optimal imaging modality of vulnerable-plaque ‘detection’ will depend on whether treatment continues to be pharmacologic plaque stabilization, in which case an overall risk of vulnerable plaque would suffice, or locally directed therapy, requiring precise anatomic definition.

Ultimately, population screening with traditional risk factors, newer serum markers, and possibly gene chips will define a group of high-risk patients in whom noninvasive imaging is appropriate. Features of plaque vulnerability detected noninvasively might justify invasive modalities. Currently, however, the optimum approach to vulnerable-plaque detection incorporates structural definition of a high-resolution modality, such as OCT or intravascular MRI, with biologic processes detected by spectroscopy or thermography.

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References


58. Moreno PR, Laddar RA, Parishothaman KR, Charash WE, O’Connor WJ. Detection of lipid pool, thin fibrous cap, and inflammat


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Briain MacNeill, Briain D. MacNeill, Harry C. Lowe, Masamichi Takano, Valentin Fuster and Ik-Kyung Jang

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