Intravascular Detection of the Vulnerable Plaque

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Coronary heart disease (CHD) remains the leading cause of death in the United States, and an estimated 1.4 million Americans have a heart attack each year. Over the past 2 decades, the concept of the “vulnerable plaque” (VP) being responsible for the majority of acute coronary syndromes (ACS) has become widely accepted. Coincidentally, there has been rapid expansion of coronary imaging modalities, both invasive and noninvasive, seeking the ability to detect high-risk plaques before their disruption and formation of occlusive thrombus. Histological characteristics of the plaques that are vulnerable to rupture are thin fibrous cap (<65 μm), large lipid pool, and activated macrophages near the fibrous cap, all of which can be detected with high-resolution coronary imaging.1 Cellular mechanisms associated with plaque instability include inflammation, reduced collagen synthesis, local overexpression of collagenase, and smooth muscle cell apoptosis. These pathological processes can alter the plaque surface and its mechanical properties, which also have been targets of recent research. Noninvasive tests, such as CT and MRI are limited by low resolution and are unable to visualize most of the features of VP. At present, only intravascular modalities can potentially distinguish VP from benign types of plaques. In this review, we focus on the recent data from the various types of intravascular modalities currently available or in development and compare their advantages and limitations.

Invasive Imaging Techniques

Coronary plaque develops eccentrically, and increasing plaque volume induces positive remodeling of the vessel, resulting in external elastic membrane expansion and preservation of luminal area. Coronary angiography only visualizes the coronary lumen and does not provide any information about the characteristics of the arterial wall and its contents. For this reason, coronary angiography has failed as a diagnostic modality for detection of VP, which often causes only modest luminal narrowing.

Various histological plaque components have been targeted as potential candidates for plaque vulnerability. These candidate features and comparisons of the invasive imaging modalities are listed in the Table.2 The characteristic architecture of a thin-cap fibroatheroma (TCFA) overlying a lipid pool has promoted further enhancements in high-resolution imaging modalities, including integrated backscatter intravascular ultrasound (IB-IVUS), virtual histology IVUS (VH-IVUS), optical coherence tomography (OCT), and intravascular MRI (IV-MRI). Plaque composition also affects the response of the vessel wall to pulsatile changes in blood pressure, and the mechanical strain patterns can be measured with elastography and palphotopy. The cholesterol-rich lipid core underlying the fibrous cap is identifiable by angiographically detected color changes reflected on the plaque surface and by the unique absorption of energy of its cholesterol crystals, leading to the development of Raman spectroscopy (RS) and near-infrared spectroscopy (NIRS). Temperature heterogeneity arising at foci of plaque inflammation has promoted the development of intracoronary thermography. Here, we present an overview of the salient features of each of these imaging modalities, their clinical applications, and their limitations.

IVUS and Its Derivatives

Grayscale IVUS

Conventional grayscale IVUS images permit an accurate determination of vessel and lumen dimensions and the distribution, morphology, and severity of the atherosclerotic plaque. Conventional IVUS is limited, however, in its ability to characterize the plaque components that determine vulnerability. Automatic processing uses the amplitude of the backscattered echo signal to differentiate highly echogenic components (calcium, dense fibrous tissue) from echolucent ones (lipid, necrotic core) but is unable to accurately distinguish fibrous from fatty plaque.3 It is generally accepted that grayscale IVUS is not capable of distinguishing plaque types. VH-IVUS and IB-IVUS use frequency data from the backscattered IVUS signal to enhance differentiation of the major plaque components.

VH-IVUS

VH-IVUS uses an autoregression model to generate multiple spectral parameters of the backscattered ultrasound signal (maximum power, corresponding frequency, minimum

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power, corresponding frequency, slope, y intercept, midband fit, and integrated backscatter). These parameters are used in classification trees to generate a tissue map of the plaque components: fibrous (dark green), fibrofatty (yellow-green), necrotic core (red), and dense calcium (white) (Figure 1). VH-IVUS data are collected during a single IVUS pullback using the Volcano Eagle Eye Gold Catheter (Volcano Corporation; Rancho Cordova, CA).

The VH-IVUS algorithm has been validated against histology in autopsy specimens and found to have an accuracy of 79.7%, 81.2%, 85.5%, and 92.8% in detecting fibrous, fibrofatty, necrotic cores, and calcium, respectively. In vivo, VH-IVUS has been performed before and after directional atherectomy in 30 patients, and a tissue map of the explanted specimen was predicted based on comparison of the 2 images. The VH-IVUS map successfully predicted the histology of the specimen with an accuracy of 87.1%, 87.1%, 88.3%, and 96.5% for fibrous, fibrofatty, necrotic core, and calcium, respectively.

Given its relative ease of use, VH-IVUS has been increasingly used as an in vivo surrogate for histological analysis. Because the VH-IVUS axial resolution of 250 μm (phased array) is insufficient to directly measure the thickness of the fibrous cap, a VH-IVUS-derived TCFA has instead been defined as a necrotic core-rich (>10%) plaque without evident overlying fibrous tissue and with a percent plaque volume of 40% seen on at least 3 consecutive images. VH-TFCAs cluster around the proximal segments of the arteries, have been found to have a similar plaque volume and necrotic core composition, and are more often associated with positively remodeled arteries than negatively remodeled ones.

VH-TFCAs have been found more frequently in patients with ACS than in patients with stable angina. In the largest study of 318 patients, those with ACS had more unstable plaques (ruptured plaques or VH-TCA) than those with stable angina (89% versus 62%; P<0.001). Excluding culprit lesions, VH-TCA was found in 65% of patients with ACS versus 36% with stable angina in a study of 91 patients.

VH-IVUS has also been used in vivo to document regression of the fibrofatty and necrotic core components of plaques after treatment with statins. Larger necrotic cores by VH-IVUS have been associated with distal embolization and no-reflow phenomenon after coronary intervention.

Recently, the validity of VH-IVUS has come into question. In a swine atherosclerosis model, there was no correlation between VH-IVUS-identified necrotic core and histology. However, it is important to note that swine necrotic cores lack cholesterol crystals, making them inherently different from human necrotic cores. Aside from the validity and technical issues that the study generated, the real question is whether identification of VP even matters. The recently presented results of the Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) trial provided the first prospective natural history study of VP. In this study, 700 patients with successful percutaneous coronary intervention (PCI) underwent 3-vessel coronary imaging with quantitative angiography, grayscale IVUS, and VH-IVUS. Palpography also was performed in a subset of 350 patients. In follow-up, clinical events were equally attributable to recurrence at the culprit lesion and new events from nonculprit lesions. Independent predictors for clinical events from nonculprit lesions (mainly progressive or unstable angina and rarely cardiac death, arrest, or myocardial infarction [MI]) were found to include a minimal luminal area <4.0 mm² (odds ratio [OR], 2.77; P=0.007), a VH-TCA (OR, 3.00; P=0.0002), and a plaque burden at the minimal luminal area of >70% (OR, 4.99; P<0.0001) (data presented at the Transcatheter Cardiovascular Therapeutics 2009, September 24, 2009; San Francisco, CA, conference). Although IVUS and VH-IVUS were able to predict clinical events, the majority of the events were unstable angina rather than cardiac death, arrest, or MI. Because the diagnosis of unstable angina can be made easily by careful history, the value of IVUS and VH-IVUS for this indication is questionable.

### IB-IVUS

Conventional grayscale IVUS is not able to distinguish the individual components of atherosclerotic plaque because of its resolution limitations, operator-dependent parameters, and automated backscatter signal processing. As a consequence, several techniques using mathematical manipulation of the ultrasound backscatter signal have been developed to im-

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**Table. Comparison of Invasive Diagnostic Modalities for Detection of VP**

<table>
<thead>
<tr>
<th>Imaging Modality</th>
<th>Resolution</th>
<th>Penetration</th>
<th>Fibrous Cap</th>
<th>Lipid Core</th>
<th>Inflammation</th>
<th>Calcium</th>
<th>Thrombus</th>
<th>Current Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grayscale IVUS</td>
<td>150–250 μm</td>
<td>Good</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>CS/CA</td>
<td></td>
</tr>
<tr>
<td>VH-IVUS</td>
<td>200–250 μm</td>
<td>Good</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>CS/CA</td>
<td></td>
</tr>
<tr>
<td>IB-IVUS</td>
<td>150 μm</td>
<td>Good</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>CS/CA</td>
</tr>
<tr>
<td>Angioscopy</td>
<td>UK</td>
<td>None</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>CS/CA</td>
</tr>
<tr>
<td>OCT</td>
<td>10–15 μm</td>
<td>Poor</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>CS/CA</td>
</tr>
<tr>
<td>RS</td>
<td>N/A</td>
<td>Poor</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>CS/CA</td>
</tr>
<tr>
<td>NIRS</td>
<td>N/A</td>
<td>Poor</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>CS/CA</td>
</tr>
<tr>
<td>Thermography</td>
<td>0.5 mm</td>
<td>N/A</td>
<td>–</td>
<td>–</td>
<td>+++</td>
<td>–</td>
<td>–</td>
<td>CS/CA</td>
</tr>
<tr>
<td>IV-MRI</td>
<td>160 μm</td>
<td>Good</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>CS/CA</td>
</tr>
</tbody>
</table>

CA indicates clinically approved for commercial use; CS, clinical studies; N/A, not applicable; UK, unknown. Data derived from MacNeill et al.²
prove the ability of IVUS to detect VP. One of these techniques is IB-IVUS imaging (Figure 1).\textsuperscript{16} Fast Fourier transformation of IVUS radiofrequency backscatter extracts frequency components of a signal buried in the original IVUS signal. IB is the averaged power of the Fast Fourier-transformed IVUS radiofrequency backscatter signal from a small volume of tissue. IB values for the various plaque components can then be calculated to construct color-coded IB-IVUS maps.\textsuperscript{16}

IB tissue maps originally were constructed from IVUS pullbacks on 18 ex vivo autopsy coronary segments, and correlation with histological analysis was performed.\textsuperscript{16} From this work, IB-IVUS maps were subdivided into 5 categories: thrombus, intimal hyperplasia/lipid core, fibrous, mixed, and calcified. The angle dependence of IB scatter signal from some plaque components also provides a method by which IB-IVUS can distinguish plaque components.\textsuperscript{17} Directive angle dependence is where there is strong angle-dependent backscatter signal such that the IB signal falls abruptly when the insonant beam is moved and is characteristic of fibrous or calcified plaque, whereas nondirective angle dependence is characterized by little change in backscatter signal with alterations in insonant beam, indicative of fatty/lipid-rich plaque.\textsuperscript{4,18}

An autopsy-based study of 42 coronary specimens showed the sensitivity of IB-IVUS for calcification, fibrous, and lipid-rich plaque to be 100%, 94%, and 84%, respectively, which compares favorably with OCT (100%, 98%, and 95%, respectively) and conventional IVUS (100%, 93%, and 67%, respectively).\textsuperscript{19} When compared with VH-IVUS, IB-IVUS provided higher diagnostic agreement with histological assessment.\textsuperscript{5}

In addition to identification of plaque components, IB-IVUS has demonstrated serial changes in plaque morphology. Reduced fibrous content, increased lipid content, and increased plaque burden have been observed with IB-IVUS in patients with initial stable angina pectoris who progress to develop ACS.\textsuperscript{20,21} IB-IVUS also has demonstrated that posi-
tive remodeled vessels are associated with higher total lipid volumes and lower total fibrous volume. Further, conversion of vulnerable lesions into more stable lesions in patients treated with statin therapy, as characterized by decreases in lipid pool content and an increase in fibrous tissue content without significant change in actual plaque burden, have been observed with IB-IVUS.\textsuperscript{7,20}

IB-IVUS is not sufficiently sensitive to distinguish intimal hyperplasia from lipid pool. There can be false-positive findings for both lipid pool and intimal hyperplasia and for fibrous versus calcified plaque due to reflectivity and attenuation.\textsuperscript{16,21} Other limitations that apply include the ex vivo validation of the technique based on histological specimens of 4-\textmu m cross-sectional thickness (IB-IVUS images represent 300-\textmu m thickness), effects of fixation and histological stains on the correlation of plaque components to IB-IVUS signals, in vivo effects of motion (catheter, cardiac, and blood) and the limited available data on reproducibility of the technique.\textsuperscript{21} Despite these limitations, there is growing research interest, primarily in Japan, in bringing IB-IVUS to the forefront of VP imaging.

**IVUS Elastography and Palpography**

Mechanical stress is caused by the pulsatile intravascular blood pressure that strains the vessel wall.\textsuperscript{23,24} The mechanical strain properties of the arterial wall reflect the components within its layers. Softer areas of tissue deform more than harder areas of tissue, potentially allowing differentiation of soft, fatty plaque regions from hard, fibrous or calcified areas of plaque.\textsuperscript{23,24} The strain properties of an atherosclerotic artery can be measured with IVUS using elastography and palpography techniques.

Radiofrequency signals are recorded at 2 different intravascular pressures at 1 location, and the local radial strain rates are determined for multiple layers of the artery, allowing for the creation of a color-coded image of the strain pattern overlaid on the area of plaque. The IVUS elastography technique has been tested in explanted human coronary and femoral arteries with a high sensitivity and specificity for the detection of fatty plaque.\textsuperscript{25} In the only clinical study of the technique, IVUS elastography data were collected on 12 patients undergoing PCI.\textsuperscript{26} Systemic pressure was used to strain the tissue, and the estimate of strain was obtained using cross-correlation of sequential frames. Calcified plaques by IVUS had a strain of 0.20\% compared with 0.51\% in noncalcified tissue. This study demonstrated the feasibility and reproducibility of the data collection in vivo, albeit without comparison to a pathological gold standard.

Intravascular palpography uses the same cross-correlation analysis of radiofrequency ultrasound signals to measure local strain along the luminal border of the artery. This local strain pattern is displayed as a color-coded palpogram superimposed on the IVUS image, allowing the identification of vulnerable “shoulders” of TCFA.\textsuperscript{24} Palpography can identify areas of high strain that are highly sensitive and specific (89\%) for TCFA in postmortem specimens.\textsuperscript{24} In vivo, highly distensible plaques by palpography have been positively correlated with the presence of yellow plaque by angioscopy, which is associated with a higher risk of rupture.\textsuperscript{27} Clinical studies have demonstrated significantly higher numbers of “high strain spots” or deformable plaques in patients with unstable angina or acute MI than patients with stable angina. The increased frequency of deformable plaques correlates with markers of vascular inflammation, such as high sensitivity C-reactive protein and lipoprotein(a).\textsuperscript{28}

The radial resolution of palpography is 400 \textmu m, which is less than elastography. The longitudinal resolution and 3D reconstruction of palpography data also are limited by the heart rate of the patient and the IVUS pullback speed. To try and improve the resolution, data set acquisition is limited to diastole triggered from the R wave of the ECG.\textsuperscript{23,24} Potential sources of error in both elastography and palpography measurements include catheter motion during acquisition, resulting in decorrelation errors; structural decorrelation noise due to signal scatter in all coordinate directions (not just back to the catheter transducer); random noise from electronic noise; and digitization noise.\textsuperscript{23,24} However, despite these reservations, IVUS palpography appears more robust and simpler to implement than elastography. IVUS palpography has been investigated in 350 patients in the PROSPECT trial described earlier, but the results have yet to be presented.

**Angioscopy**

Angioscopy applies fiber-optic technology to directly visualize the luminal surface and is able to characterize plaque composition on the basis of luminal appearance and to distinguish between white and red thrombus. Endoluminal irregularities such as ulceration, fissures, and tears also can be seen.

Angioscopy describes the appearance of the luminal surface based on color (Figure 2).\textsuperscript{29} A normal coronary artery appears as glistening white, whereas atherosclerotic plaque can be categorized as yellow or white. Histopathologic data support the association of yellow color with high concentrations of cholesterol-laden crystals with or without plaque degeneration.\textsuperscript{30} The intensity of yellow color also is an indicator of fibrous cap thickness, with high yellow intensity associated with thin, fibrous caps overlying a lipid core. In a comparison study using angioscopy and OCT, the sensitivity and specificity of the angioscopy-identified yellow plaques for having a fibrous cap measuring \(<110\ \mu m\) by OCT was 98\% and 96\%, respectively.\textsuperscript{31} 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 represent a VP.\textsuperscript{32} In patients with MI, yellow plaques can be seen in the infarct-related segment as well as in noninfarct-related arteries, but only culprit segments have angioscopically evident thrombus.\textsuperscript{33} Further, Hirayama et al\textsuperscript{14} showed that statin therapy for 28 weeks was effective in decreasing yellow intensity by angioscopy and reducing atheroma volume by IVUS, suggesting regression or stabilization of the plaque.

The most significant limitation of coronary angioscopy is the need for a blood-free field of view. One method of creating a blood-free field is to occlude the vessel proximally with a balloon; however, this method carries the risk of
inducing myocardial ischemia and severely injuring the vessel (eg, dissection, perforation, thrombus). An alternative method is to use a small catheter to continuously flush saline in front of the angioscope to transiently displace blood, but this technique requires removal of the guidewire before image acquisition. Color interpretation is subjective and depends on the viewing angle of the plaque, and these issues have been major criticisms of coronary angioscopy. To address these shortcomings, a quantitative colorimetric technique was developed. Ishibashi et al. showed that plaque disruption was seen in 79% of lesions with high yellow color intensity (defined as $b^*$ value > 23) versus 41% of lesion $b^*$ values $< 23 (P = 0.007$) in patients with ACS. Although their findings are promising, angioscopy only images the plaque surface, and the atherosclerotic surface changes may not be sufficiently sensitive to detect subtle changes in plaque composition, features that have been raised in comparison studies of imaging modalities.

OCT

OCT is the optical analog of IVUS. It measures backscattered light or “optical echoes” reflected off the arterial wall. OCT uses low coherence, NIR light that is emitted from a superluminescent diode. The image is created based on reflection time and the intensity of the backscattered light. OCT has an axial resolution of $\approx 10 \, \mu m$, which has been validated ex vivo, and because of its superior resolution capabilities, it is capable of visualizing many of the morphological features of VP (Figure 3). OCT characteristics of 3 plaque morphologies have been established with ex vivo histological correlation as follows: Sensitivity and specificity detected for fibrous plaques (homogeneous, signal-rich regions) were 79% and 98%, respectively; for fibrocalcific plaques (well-delineated, signal-poor regions with sharp borders), 96% and 97%, respectively; and for lipid-rich plaques (signal-poor regions with diffuse borders), 94% and 92%, respectively. OCT is the only imaging modality with high enough resolution to measure fibrous cap thickness. Another unique ability of OCT is the detection of macrophages, which are relatively large (20 to 50 $\mu m$) and are able to scatter light. In an autopsy study, OCT images of 26 lipid-rich segments were correlated with histology, and OCT was able to detect an arbitrarily defined cap macrophage density $> 10\%$ with 100% sensitivity and specificity.

OCT has been studied in vivo in patients with acute and stable coronary syndromes, and the results demonstrate that plaque characteristics are associated with different clinical presentations. Lipid-rich plaque (defined by lipid occupying $\approx 2$ quadrants of the cross-sectional area) was observed in 90% of patients with ST-elevation MI, 75% of patients with non-ST-elevation MI or unstable angina, and 59% of patients with stable angina. The same study also showed that fibrous cap thickness was significantly thinner in patients with ACS versus those with stable coronary artery disease. Lipid-rich plaques identified by OCT have been associated with increased incidence of no-reflow phenomenon, and the size of the lipid arc was an independent predictor for no-reflow.

Figure 2. Classification of plaques according to the yellow color intensity: grade 1, light yellow; grade 2, yellow; and grade 3, intensive yellow. Reproduced with permission from Ueda et al.

Figure 3. OCT images. A, Fibrous plaque (*). B, Lipid tissue (*) under fibrous cap. The fibrous plaque thickness at the thinnest part (arrow) is 130 $\mu m$. C, Lipid plaque (*) with very thin fibrous cap (arrow). Minimal thickness of the fibrous cap is 20 $\mu m$. Arch of the lipid was measured as an angle between the 2 straight lines that joined the center of lumen to both ends of lipid area. D, Protruding thrombus (arrow) overlying thin-cap lipid plaque (*). Reproduced with permission from Takano et al.
OCT has been used to show that statin therapy can increase fibrous cap thickness as early as 9 months after acute MI. Similarly, the relationships between peripheral white blood cell count, cap macrophage density, and presence of TCFA have been studied in patients with acute and stable coronary artery disease. This study demonstrated that peripheral white blood cell count correlated with cap macrophage density, and both of these parameters independently and particularly in combination predicted the presence of TCFA. In a study combining plaque characteristics obtained by IVUS and OCT, plaques with positive remodeling compared with absent or negative remodeled plaques were more commonly associated with lipid-rich plaque, TCFA, and higher macrophage density. On the basis of these findings, OCT has emerged as the most promising imaging modality in visualizing the morphological features of VP.

Limitations of OCT are related predominantly to the features of a light-based energy source, which include poor tissue penetration and interference from blood. OCT has a penetration depth of 2 to 3 mm, which prohibits imaging beyond the internal elastic lamina. Blood also absorbs light and must be replaced before OCT imaging. This replacement can be achieved with saline or lactated Ringer solution infusion with or without balloon occlusion. Newer frequency-domain OCT systems allow for faster pullback imaging (15 versus 1 mm/s) that can be coupled to power injection of radiopaque contrast, obviating the need for proximal balloon occlusion and, therefore, decreasing the potential for ischemic complications. An additional limitation of OCT is that it is not always obvious to distinguish lipid from calcium. Both lipid and calcium create signal-poor regions, and the only difference between them is the border characteristics (lipids have diffuse borders, and calcium has sharp borders). Comparison studies with other imaging modalities may be helpful in improving the diagnostic criteria between lipid and calcium.

Spectroscopy

Spectroscopy, the study of energy wavelengths, is used routinely in physical science to determine the chemical composition of substances. A spectrum of a given molecule is unique, enabling these techniques to identify the chemical composition of a subject. Spectra are created by processing the collected light scattered from an artery that is emitted during laser or infrared light illumination. Plaque components such as cholesterol and calcium have unique absorption and reflectance patterns of light, also referred to as diffuse reflectance spectroscopy. To date, the most validated spectroscopy methods are RS and NIRS.

RS is based on the unique laser light wavelength shifts reflected off a substance, also referred to as Raman shift. The molecular characteristics of lipid and calcium and their unique Raman shift patterns make RS highly sensitive for plaque detection. A diagnostic algorithm has been constructed based on fit contributions of the independent spectra of the various chemical constituents of atherosclerotic plaque, and this algorithm was validated to classify coronary artery plaques with a specificity of 94%.

A major limitation of RS is that only a small number of photons are recruited into the Raman shift, resulting in poor tissue penetration and low signal-to-noise ratio. Additionally, background noise from backscattered light within the optical fibers of the catheter-based system also degrades signal quality. A newer technique has been shown to significantly reduce these background signals by looking in the high wavenumber Raman region (2400 to 3800 cm

NIRS measures diffuse reflectance signals by using NIR light (wavelengths from 800 to 2500 nm) as an energy source. An NIRS spectrometer emits light onto a substance and measures the light that is reflected back over a wide range of optical wavelengths; this information then is processed to produce a spectrum. Spectra obtained from a scan are applied to an algorithm that predicts the probability of VP and are displayed on a chemogram (Figure 4), with lipid pools colored yellow in a background of red. Recently, the NIRS system was validated in vivo in 106 patients undergoing PCI. This study showed that in 40 of the 48 patients, there was spectral similarity compared to spectra obtained from autopsy specimens. The major advantage of NIRS is that imaging can be performed without replacing the blood in the vessel, which is required for OCT. However, the major limitations of NIRS are that it only detects one characteristic of VP and is unable to determine depth, superficial versus deep, of the lipid core. Catheters that provide multimodality imaging by combining NIRS and IVUS are now commercially available.

IV-MRI

MRI techniques are able to evaluate tissue structure and composition throughout the human body with excellent spatial resolution. It has been used successfully to assess plaque size and characteristics in the aorta and carotid arteries. Imaging VP with surface MRI is inadequate because of low signal-to-noise ratio. Invasive IV-MRI has been developed as a technique to overcome these limitations. There are 2 MRI methods: one uses intravascular receiver coils, and the other uses a self-contained MRI probe. IV-MRI with a 0.03-inch intravascular receiver coil in the iliac artery coupled with a 1.5-T scanner can readily differentiate fibrous, lipid, and calcified tissue with a spatial resolution of 312 μm. Unfortunately, this spatial resolution is not sufficient to measure TCFA. The need for an external magnet and scanner, bulkiness of the coil catheter, and heat production are major limitations prohibiting coronary imaging with this technique. The alternative technique is the use of an intravascular probe that has a self-contained magnet and transmitter/receiver coils. Static magnetic gradients are generated at the lesion of interest, and these gradients are responsive to the diffusion properties of the plaque and its constituents. In the presence of a magnetic field gradient, the protons carried by water molecules undergo a phase shift. Self-diffusion is characterized by random (Brownian) displacements of water mole-
...cles, and attenuation of MR signal occurs when phase shifts interfere with one another. Self-diffusion is affected by temperature and the molecular environment, and therefore, fibrous and lipid-laden tissues could be differentiated on the basis of their apparent water diffusion coefficients (ADC). Fibrous tissue is characterized by nonrestricted self-diffusion, fast decay of MR signal, and high ADC, whereas lipid-rich tissue is characterized by restricted self-diffusion, slow decay of MR signal, and low ADC. On the basis of the scan, a lipid fraction index is generated. The IV-MRI probe field of view is 2 mm in length, has up to a 120° circumferential view, and has a penetration depth of 250 μm. An ex vivo study showed a 95% sensitivity and 100% specificity for the IV-MRI probe, and the first-in-man application for the device demonstrated safety with no complications at 30 days. Similar to NIRS, a major limitation of IV-MRI probe is that it does not produce a real image, but the computer-generated image is a chemical signature of only one characteristic of VP.

**Thermography**

Another hallmark feature of VP is an inflammatory reaction manifested by the local invasion of macrophages and lymphocytes and the deposition of matrix metalloproteinases that degrade the supporting collagen leading to plaque fragility. This intense inflammatory process creates local temperature elevations of the plaque surface, which can be measured with a catheter-based thermistor with a temperature differentiation of 0.05°C and spatial resolution of 0.5 mm. In vivo studies have shown that temperature differences between plaque and normal wall and temperature heterogeneity (TH) can be measured in human coronary atherosclerotic plaques. TH was absent in normal coronary arteries, whereas it increased progressively from stable angina to acute MI, with TH seen in 20%, 40%, and 67% of the patients with stable angina, unstable angina, and acute MI, respectively. Furthermore, a prospective study showed that high temperature differentials were associated with increased adverse events after PCIs. Thermography also has been shown to delineate the site of culprit plaque and has shown that maximal temperature site is usually distal to the angiographically most-stenotic site. Further, patients treated with atorvastatin had statistically significant lower temperature differences than untreated patients, bolstering the concept that statin therapy has an antiinflammatory effect in addition to lowering lipids. These studies in culmination provide validation that modalities to detect local temperature as a surrogate marker for inflammation may be useful in localizing VP. Studies also have combined IVUS and thermography, and the combination of anatomy and physiology may provide additional diagnostic and prognostic information.

One potential pitfall to this technique is that it requires direct contact with the arterial wall, which raises the possibility of vessel injury and its consequences. Another pitfall is the issue of the diagnostic accuracy of temperature measurements by thermography. There appears to be a significant overlap between temperature differentials in stable and unstable presentations of coronary artery disease. Additionally, there is no conclusive evidence that temperature differentials or TH are related to plaque vulnerability. Further, a recent study showed that variations in coronary pressure and blood flow alter the temperature measurements with a thermistor, and temperature elevations observed in previous studies may have been due to artifact. This study raises the validity of the findings on all previous thermography studies.

**Future Role of Intravascular Detection of VP**

The value of a diagnostic technique depends on ease of use, cost, accuracy, and the availability of effective therapeutic options. Because of their invasive nature and high cost, the current intravascular techniques discussed in this review are not appropriate screening tools for identifying high-risk individuals for imminent coronary events, such as acute MI or
sudden cardiac death. Therefore, there is no apparent role of the invasive diagnostic tools for primary prevention at the present time.

Whether these techniques can be used for secondary prevention is also unclear. For complete screening of VP, all 3 coronary trees need to be probed at the time of cardiac catheterization, which would prolong procedure time, increase cost, and increase the risk of procedure-related complications. Furthermore, the definition of VP and its natural history are not yet firmly established. In the PROSPECT trial (the only natural history study using intravascular imaging to date), the rate of MI for nonculprit lesions was very low (1% in 3 years). Similarly, low rates of MI were seen in 2 studies using physiological lesion assessment by fractional flow reserve (FFR) measurement. The recently published 2-year outcomes of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study demonstrated that of the 509 patients who had a deferred lesion (angiographic ≥ 50% stenosis and FFR > 0.80), only 1 (0.2%) had a MI in an originally deferred lesion.61 In the DEFER (Deferral Versus Performance of PTCA in Patients Without Documented Ischemia) study, none of the patients in the defer group (FFR ≥ 0.75) had an MI at 5 years.62 Conversely, higher rates of cardiac death or MI were observed in vessels that had an ischemic FFR. These studies suggest that the most important prognostic factor in determining vulnerability may be the presence of inducible pressure loss across a lesion.

The invasive nature of these tests and the low rates of hard clinical events despite identification of a potentially high-risk plaque make it difficult to design clinical trials aiming to reduce or prevent coronary events and undermine the utility of the imaging modalities discussed in this review. Each imaging modality has its strengths and weaknesses, and therefore, each has its own surrogate definition for VP. It may turn out that the best method to image VP will be to combine techniques, and in fact, combination catheters currently are in development.

It is important to remember that atherosclerosis is a continuous process of plaque disruption and healing, and in fact, most plaque ruptures are clinically silent. Plaque morphology is only one factor that determines a plaque’s fate, with a dynamic relationship among local structural changes, thrombotic stimulus of the plaque disruption, and systemic coagulation status also contributing. Thus, it is unlikely that morphological features alone can reliably predict the outcome for a specific plaque, and for this reason, trials like PROSPECT are unlikely to show significant benefit. Because of the lack of evidence from clinical trials showing any benefit of VP identification, intravascular imaging for VP should not be performed routinely. Prospective observational trials and registries that use these intravascular imaging modalities are ongoing, which hopefully will elucidate the relationships among morphology, clinical factors, and outcomes.

Then, what is a potential role of these intravascular diagnostic techniques? Until outcomes data can support their clinical use, the only role for intravascular imaging is for research. In particular, one potential application could be to evaluate novel pharmacological interventions targeted to plaque stabilization and plaque volume reduction. For example, a drug that is designed to stabilize plaques can be evaluated in its ability to modify VP characteristics, such as fibrous cap thickness, lipid concentration, macrophage density, and vascular remodeling, in a small cohort of patients before being studied in mega clinical trials. In other words, these invasive modalities can be screening tools to save money and time to select the most effective new therapies for larger clinical outcome trials.

**Conclusion**

Several modalities have been validated and are under investigation for their potential role for detection of VP. Although it looks unlikely that current technology can provide enough information, the combination of different technologies, including imaging, physiological tests, and serum/genetic tests, may make it possible to detect VP. If it becomes a reality, local therapy delivery can be easily combined with catheter-based diagnostic tools.

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