Frontiers in Intravascular Imaging Technologies

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In 1971, Bom et al developed one of the first catheter-based real-time imaging techniques for use in the cardiac system. In placing a set of phased-array ultrasound transducers within the cardiac chambers, Bom and colleagues showed that higher frequencies than those used in transthoracic ultrasound imaging could be used to produce high-resolution images of cardiac structures. By the late 1980s, Yock et al had successfully miniaturized a single-transducer system to enable transducer placement within coronary arteries. Since then, intravascular ultrasound (IVUS) has become a pivotal catheter-based imaging technology, having provided practical guidance for percutaneous interventions and scientific insights into vascular biology in clinical settings. Technical developments currently being explored consist of further device improvements, a variety of advanced image analyses, and the extension of this ultrasound-based approach to diverse intravascular imaging techniques with other energy sources.

Principles and Device Developments

Ultrasound-Based Approaches

IVUS systems produce tomographic images by performing a series of pulse/echo sequences, or vectors, in which an acoustic pulse is emitted and the subsequent reflections from the tissue are detected. Each vector is acquired by directing the ultrasound beam from the catheter in a slightly different direction from the previous vector by mechanical or electrical means. A gray-scale IVUS image is made with all the vectors (commonly 256 vectors), with each vector acquired at a different angle of rotation.

Several clinically relevant properties of the ultrasound image, such as the resolution, depth of penetration and attenuation of the acoustic pulse by tissue, are dependent on the geometric and frequency properties of the transducer. A crystal transducer emits a signal that spans a range of frequencies. The higher the center frequency, the better the radial resolution (Figure 1) but the lower the depth of penetration. Conventional IVUS catheters used in the coronary arteries have center frequencies that range from 20 MHz to 40 MHz, thus providing theoretical lower limits of resolution (calculated as half the wavelength) of 39 and 19 μm, respectively. In practice, the radial resolution is at least 2 to 5 times poorer, as determined by factors such as the length of the emitted pulse and the position of the imaged structures relative to the transducer.

For peripheral and intracardiac echocardiographic (ICE) applications, larger imaging catheters with lower center frequencies (8 to 20 MHz) are produced in both mechanical and electrical configurations. In addition, a phased-array intravascular echocardiography catheter is available that provides a sector image with color/spectral Doppler and multiple frequency imaging (5.0 to 10 MHz) capabilities.

Optical Approaches

Angioscopy

Intracoronary angioscopy is an endoscopic technology that allows direct visualization of the surface color and superficial morphology of atherosclerotic plaque, thrombus, neointima, or stent struts. The light source emits a high-intensity white light to illuminate the target object through the fiber optic catheter. The imaging catheter contains a flexible fiber optic bundle of several thousand pixels; the latest-generation catheter, which incorporates 6000 fibers, is 0.75 mm in outer diameter with a microlens that provides a 70° field of view and a focused depth that ranges from 1 to 5 mm. Although conventional delivery systems were equipped with a distal balloon to create a blood-free field for optical imaging, an alternative system uses a smaller catheter to continuously flush an optically clear liquid in front of the tip of the angioscope for transient blood displacement. To circumvent the subjectivity of color interpretation, quantitative colorimetric methods have been proposed. One research group is also developing a side-view imaging catheter to overcome several inherent limitations of the conventional forward-view catheter configuration (Figure 2).

Optical Coherence Tomography

Optical coherence tomography (OCT) generates real-time tomographic images from backscattered reflections of infrared light. The greatest advantage of this optical technology is its resolution that is significantly higher (10 to 15-μm axial resolution and 20 to 25-μm lateral and out-of-plane resolution) than ultrasound-based approaches. This improvement comes at the expense of poorer penetration through blood and tissue (1 to 3 mm). The imaging catheter includes a fiber optic core with a microlens and a prism at the distal tip to generate a focused scanning beam perpendicular to the catheter axis.
The current OCT catheter has a stationary outer sheath so that the inner imaging core can rotate safely to provide cross-sectional images. This design also facilitates an automated pullback of the imaging core. At present, 1 company (LightLab Imaging Inc, Westford, Mass) has commercialized intravascular OCT technology by providing dedicated imaging wires and occlusion balloon catheters.

In standard OCT systems (time-domain OCT), the optical engine includes a superluminescent diode as a source of low-coherent infrared light, typically with a wavelength around 1300 nm. The high propagation speed of light requires OCT to use interferometric techniques to determine the depth of the reflector.

To reduce ischemia during blood-free optical imaging, several groups have been developing rapid-scan OCT systems, referred to as Fourier-domain OCT or optical frequency domain imaging. This technique measures optical echo time delay by use of a light source whose light output can be rapidly swept over a range of wavelengths (eg, 1260 to 1360 nm). Fourier transform techniques enable conversion of the frequency domain (or wavelength-dependent) data to a time-domain representation. Although conventional time-domain systems have a frame rate of 4 to 20 frames per second, frequency-domain OCT achieves acquisition at 80 to 110 frames per second, which allows for comprehensive scanning of long arterial segments during a short balloon occlusion or even 1 bolus liquid flush without occlusion. The first clinical study with this technology is being initiated to investigate vulnerable plaque hypotheses in a prospective multicenter fashion.

**Intravascular Spectroscopy**

Spectroscopy determines the chemical composition of plaque substances based on analysis of spectra induced by interaction of light with the tissue materials. To date, several forms of photonic spectroscopy have been adapted for tissue characterization, including diffuse reflectance near-infrared (NIR), Raman, and fluorescence spectroscopy. When tissues are exposed to a light beam that contains a broad spectrum of wavelengths, wavelengths absorbed by the illuminated molecules will be missing from the spectrum of the original light after it has traversed the tissue. Diffuse reflectance NIR spectroscopy analyzes the amount of this absorbance as a function of wavelengths within the NIR window (700 to 2500 nm; Figure 3). In contrast, Raman spectroscopy uses a light beam of a single wavelength and monitors shifts in wavelength as some of the incident photons interact with the molecules in the tissue and gain or lose energy. Raman spectroscopy measures this inelastic scattering (shift in wavelength) because it contains unique information on the substance with which the photons interacted. Under a certain condition, the photons can excite molecules to a higher energy level, the decay from which releases the energy difference in the form of light. Fluorescence spectroscopy utilizes photoluminescence or luminescent emission to identify the properties of the tissue being illuminated.

For diffuse reflectance NIR spectroscopy, a coronary catheter system is under clinical evaluation for commercial use (InfraReDx, Inc, Cambridge, Mass). The 3.2F rapid-exchange NIR catheter contains fiber optic bundles for delivery and collection of light within a protective outer sheath. The catheter directs the light to the vessel wall with a mirror located at the tip, and spectra acquisition can be done at 5 ms through flowing blood.

Because of the low intensity of Raman light scattered from the vessel wall, the development of intravascular Raman spectroscopy systems is technically more challenging. One research group has developed a fiber optic probe that consists of a central fiber for laser delivery surrounded by 15 fibers for sample light collection. Both fibers have a dielectric filter to block the Raman signal generated by the fiber material. The system uses an 830-nm diode laser as a light source, and the data acquisition time has been reported as 1 second in an in vivo setting.
vivo study. To circumvent blood interference, another group developed a real-time Raman system with prototype catheters equipped with an eccentric balloon or a basket configuration, which enables gentle contact of the probe against the vessel wall. A prototype intravascular NIR fluorescence probe (0.018-in single fiber) is also being tested with animal models.

**Magnetic Resonance Imaging–Based Approaches**

Magnetic Resonance Imaging (MRI) evaluates tissue with an electromagnetic radiofrequency pulse application within a strong static magnetic field. The main advantage of MRI compared with other imaging modalities is its ability to achieve strong contrast between soft tissue components (Figure 4). However, this plaque characterization is currently limited to relatively large or superficial arteries owing to the significant falloff of signal-to-noise ratio in deeper regions imaged when an external coil is used. Cardiac motion is also a significant factor that limits the resolution of coronary artery imaging with MRI. The placement of an MRI probe within the artery is one possible solution, because it would allow a high signal-to-noise ratio at the level of the arterial wall. The addition of an MRI coil to a catheter device is useful not only for imaging but also for tracking catheter position in real-time MRI interventions.

The most common approach to intravascular MRI (IV-MRI) is the combination of an intravascular receiver coil and an external MRI scanner. Using balloon-injured hyperlipidemic rabbits, one group reported the feasibility of a nonobstructive IV-MRI coil for in vivo imaging of atherosclerosis. The intravascular probe was based on a single-loop receiver coil design and included a lumen for a 0.014-in guidewire. More recently, a significantly miniaturized detector coil (a 0.030-in wire-based device) has been validated in ex vivo and in vivo human iliac arteries. This device is made from nitinol tubing with mechanical properties similar to standard guidewires. A theoretical safety concern is the heat generation that can occur under certain circumstances during imaging; however, a recent rabbit study using a guidewire-based IV-MRI showed no abnormal changes of coagulation factors, clinical manifestations of blood coagulation disorders, or histopathological thermal damage in target vessels.

Another interesting approach is to incorporate both magnets and coils within the catheter, which would permit standalone imaging with no external scanner. The current system (TopSpin Medical, Lod, Israel) is specifically designed for tissue characterization, providing a color-coded tissue component map, rather than anatomic imaging. The first-generation probe used in pilot clinical evaluation is 1.73 mm in diameter and provides depth-of-view imaging in the radial plane of 250 μm, lateral resolution of a 60° sector, and slice thickness of 2 mm (Figure 5). To eliminate motion...
artifacts, the probe needs to be stabilized against the arterial wall by gentle inflation of a partially occlusive side balloon. A 4.5F second-generation catheter with dual sensors at 180° angular displacement is currently being developed for faster data acquisition with no manual rotation of the catheter.

### Intravascular Thermography

The concept of plaque temperature measurement as a marker of local inflammation process was originally proposed on the basis of observations from human carotid endarterectomy specimens. In an ex vivo study with a needle thermistor, intimal surface temperature correlated positively with cell density (mostly macrophages) and inversely with the distance of the cell clusters from the luminal surface.

The local vessel wall temperature can be assessed by 2 approaches: thermocouple- and infrared-based measurements. The first approach incorporates a single or multiple thermal sensors at the catheter tip and requires contact of the thermal sensors with the vessel wall. The second approach uses an infrared fiber optic catheter to provide thermal imaging without direct vessel wall contact. In either platform, one technical consideration is the influence of blood flow on measured temperature. Given a large volume of coronary blood flow, this “cooling effect” can significantly impact the acuity of this modality to detect a small thermal heterogeneity, especially in the presence of turbulent flow.

### Current Clinical Applications and Limitations

Of all the technologies, IVUS is the most mature and widely used intravascular imaging technique. To date, IVUS has provided significant insights into biologically mediated processes of the vasculature, such as the extent of plaque burden, vascular remodeling, and restenosis in patients with coronary artery disease. This technology has also been established as a significant clinical tool in the evaluation and guidance of interventional techniques, including balloon angioplasty, atherectomy, conventional stenting, brachytherapy, and most recently, drug-eluting stents (DES).

Over the past year, the use of IVUS has grown considerably, driven by recent public concerns about the safety of DES. In the era of bare-metal stents, a number of studies demonstrated that IVUS guidance could improve the outcomes of stenting by identifying several morphological or morphometric risk factors of stent thrombosis or restenosis. Importantly, recent IVUS studies have suggested that the majority of these risk factors, such as stent underexpansion and residual reference disease, continue to be significant determinants of DES failure. On the other hand, late-acquired incomplete strut apposition has been reported more frequently in DES than in bare-metal stents. Although a recent clinical study indirectly suggested a possible link of this IVUS finding with late DES thrombosis, its exact role in the pathogenesis of this rare clinical event remains unknown.

Intracoronary angioscopy is another established diagnostic modality that clinical investigators worldwide have been using to gain additional insights into the pathophysiology of coronary lesions. Because of the high sensitivity of angioscopy to detect intraluminal thrombus in vivo, as well as its unique ability to evaluate the surface color of plaque, this imaging technology has found an important clinical niche, particularly in the field of vulnerable plaque and acute coronary syndromes. More recently, several investigators have successfully used this technology for macroscopic evaluation of neointimal coverage and local thrombus formation over DES struts in clinical settings.

Both imaging modalities, however, have several technical limitations. Limited spatial resolutions do not allow direct visualization of microstructure, including endothelialization of stent surface, a thin fibrous cap over a lipid core, or microvasculature within the vessel wall. Accurate 3-dimensional (3D) image orientation, precise discrimination of tissue components, and functional assessment of vessel wall in terms of biomechanical properties or plaque activity (atherogenic or inflammatory process) would also facilitate better understanding of vascular pathology and the optimization of interventional strategies.

### Evolving Technical Advancements

#### Three-Dimensional Image Registration

Compared with external imaging methods, one technical disadvantage common to catheter-based imaging is greater difficulty in accurately determining the 3D position and orientation of the imaged structure. Thus, several groups have introduced 3D transducer navigation or tracking techniques. This can be accomplished by reconstruction of the 3D pullback trajectory with biplane radiographic recordings of
the transducer or by real-time tracking of a miniaturized electromagnetic position sensor mounted in the catheter tip (Figure 6).

The geometrically correct 3D reconstruction of vessel wall structure may not only facilitate percutaneous interventions in complex anatomy but also allow detailed in vivo profiling of intracoronary hemodynamics and endothelial shear stress. A number of pathological and experimental studies have shown that inhomogeneities and irregularities of these factors play an important role in the initiation, localization, growth, composition, remodeling, and destabilization of atheromatous plaque. A recent study with spatially correct 3D IVUS has confirmed these observations in part in a clinical setting, directly relating local endothelial shear stress at baseline to subsequent plaque progression and arterial remodeling at 6 months. The predictive value of this parameter for future coronary events awaits the result of an ongoing clinical trial (PREDICTION). Additionally, the vascular response to stent implantation is a potentially important field to investigate with this technology. Anatomically complex lesions, such as bifurcations and long lesions, are being more actively treated with DES. This approach can significantly alter vascular geometry and thus local endothelial shear stress in this particular lesion subset.

**Guidance for Percutaneous/Surgical Treatment**

**Infrared Cardiac Endoscopy**

Most optical techniques require temporary blood displacement with optically clear liquid, which may be associated with occasional procedural complications. One theoretical solution is to use longer wavelengths than the visible spectrum (400 to 750 nm) to reduce light scattering by red blood cells. The principles of this technique, derived from the Mie scattering theory, have been well studied and applied in atmospheric and military science to see through clouds, fogs, and mist. This theory predicts light scattering to be proportional to the inverse square of the wavelength; for example, infrared light at 1620 nm will encounter only one ninth the scattering as a visible wavelength of 533 nm. On the other hand, the blood absorption of infrared light is relatively large at 1350 to 1500 nm and longer wavelengths, thus the wavelength in the region of 1500 to 1850 nm theoretically represents an optimal imaging window for infrared cardiac endoscopy.

On the basis of this mathematical-physical background, prototype catheters of infrared endoscopy have been developed with infrared light in the 1600±70-nm region (Figure 7). Animal studies demonstrated the safety and feasibility of obtaining real-time in vivo images of intracardiac or vascular structures through flowing blood, with consistency among...
species and subjects. Accordingly, the US Food and Drug Administration has approved the first commercial system (Cardio-Optics, Inc, Boulder, Colo) for visual guidance of coronary sinus cannulation for cardiac resynchronization therapy. The latest imaging catheter has a 7F outer diameter and incorporates a flexible fiber optic bundle with a microlens that provides an 80° conical, forward-viewing field with a focused depth that ranges from the tip to 35 mm. The catheter is equipped with a steerable distal articulation to deflect the catheter tip, which allows the operator to turn the visual field in the desired direction. Although this modality is not a substitute for coronary angiography because of its monochromatic nature, the versatility of this core technology may offer several potential applications (eg, procedural guidance for noncoronary cardiac interventions, complex electrophysiology procedures, or minimally invasive surgical treatments).

NIR Fluorescence Angiography

NIR fluorescence angiography is another optical imaging technique for the guidance of surgical revascularization therapy. This technique utilizes the unique optical properties of indocyanine green with absorbance and fluorescence maxima in the NIR region. The imaging system consists of an imaging head that contains an 806-nm laser light source and a charge-coupled device camera with an optical filter to effectively receive indocyanine green–fluoresced light at 830 nm. After intravascular injection of indocyanine green, the system provides real-time visualization of de novo or bypass vasculature immediately before or after the bypass procedure (Figure 8), thereby enabling operators to assess the patency of anastomosis sites and distal runoff in the operating room. A recent clinical study reported that intraoperative NIR fluorescence angiography had detected significant graft problems that required major revision in 4.2% of coronary bypass graft cases.

Identification of Plaque Components

Ultrasound-Based Approaches

The majority of current IVUS-based tissue-characterization techniques use computer-assisted analysis of raw radiofrequency signals in the reflected ultrasound beam. These techniques are primarily based on the fact that more information is contained in the backscattered ultrasound signal than is revealed by conventional imaging based on signal amplitude alone. To date, a variety of signal parameters and mathematical models have been shown to enhance tissue discrimination. In an autopsy study, one group demonstrated that integrated backscatter values, calculated as the average power of the backscattered ultrasound signal from a sample tissue volume, were significantly different among tissue types. Using this technique with 3D color-coded mapping, a recent study suggested the clinical feasibility of quantitative plaque characterization, demonstrating lipid-volume reduction and a concomitant increase in fibrous tissue volume in response to treatment with statins versus placebo. Other investigators have used unique ultrasound wave properties from different tissue types, such as signal-attenuation slopes, statistical frequency distribution, and angle-dependent echo-intensity variation. Wavelet analysis, a mathematical model for assessing local wave patterns within a complex signal, has also demonstrated accurate ex vivo and in vivo discrimination of lipid-rich from fibrous plaques with histological verification in necropsy or directional atherectomy specimens.
Among these methods, one system (Virtual Histology, Volcano Therapeutics Inc, Rancho Cordova, Calif) has been commercialized and is drawing considerable attention. This technique is one of spectral radiofrequency analyses that uses a classification algorithm developed from ex vivo data sets with coronary specimens. The pattern-recognition algorithm generates color-mapped images of the vessel wall, with a distinct color for each of the fibrous, necrotic, calcific, and fibrofatty categories. When combined with automated pull-back and border-detection techniques, this system provides a quantitative assessment of each tissue category over a 3D coronary artery volume. An initial clinical study has shown a significant correlation of virtual histology–determined plaque composition with corresponding histopathology of the coronary specimens.

Other investigators reported that virtual histology–determined plaque composition was related to coronary artery remodeling, one of the morphological markers of potential plaque vulnerability. In a series of 55 patients with a nonculprit, nonobstructive (<50%) de novo lesion, virtual histology–derived thin-cap fibroatheroma, defined as focal, necrotic, calcific, core-rich (≥10% of the cross-sectional area) plaque without evident overlying fibrous tissue, was shown as a more prevalent finding in patients with acute coronary syndrome than in stable angina patients. On the other hand, controversial results also exist on the relationship between the virtual histology findings and clinical presentations (less necrotic core and more fibrous tissue in acute coronary syndromes).

Current technical limitations include limited spatial resolution (100 to 250 μm), no classifications for thrombus, blood, or intimal hyperplasia, and potential errors due to poor ultrasound penetration through extensive calcification. Among several multicenter studies initiated worldwide, PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) is one of the largest natural history trials; it used 3-vessel imaging with Virtual Histology and IVUS palpography (see below) in 700 acute coronary syndrome patients. Clinical follow-up for up to 5 years is ongoing, and the role of this technology in the detection of rupture-prone plaques is yet to be established.

Optical Approaches

Polarization-Sensitive OCT

Polarization analysis, which measures the degree of birefringence in tissue, may enhance plaque component discrimination by OCT. In general, tissues with highly oriented fibrous or smooth muscle cell components are more sensitive to the polarity of the imaging light than degenerated atheromatous tissues with randomly oriented cells and thus exhibit a property referred to as birefringence. One group calculated the magnitude of tissue birefringence from polarization-sensitive OCT of human aortic specimens by measuring the phase retardation caused by the different velocities of polarized lights within birefringent tissues. The measurements of birefringence correlated significantly with both collagen fiber content (Figure 9) and smooth muscle cell density within plaques and in fibrous caps of necrotic core fibroatheromas.

Given the significance of collagen degradation in plaque destabilization, polarization-sensitive OCT may provide important information on structural factors involved in risk stratification of coronary lesions. It may also be helpful in improving the accuracy of fibrous cap–thickness measurements.

Spectroscopy

Using diffuse reflectance NIR spectroscopy, one group recently compared the findings of human aortic samples with corresponding histology. The sensitivity and specificity of NIR spectroscopy for histological plaque vulnerability were 90% and 93% for lipid pool, 77% and 93% for thin fibrous cap (<65 μm), and 84% and 89% for inflammatory cell infiltration, respectively. Similarly promising results of NIR spectroscopy to identify lipid-rich plaques have also been reported in human carotid endarterectomy and coronary.
autopsy specimens. Although these ex vivo studies were performed in a blood-free laboratory setup, an in vivo rabbit aortic study showed the feasibility of intravascular NIR spectroscopy through blood by identifying lipid areas >0.75 mm² with 78% sensitivity and 75% specificity.

Although Raman spectroscopy has a theoretical advantage in direct quantification of individual plaque components, only a small percentage of photons are recruited into the Raman shift, which results in low signal-to-noise ratio and poor tissue penetration. However, use of an NIR wavelength laser (750 to 850 μm), coupled with enhanced charge-coupled device array cameras, could significantly improve the signal-to-noise ratio. In addition, mathematical tools have been developed to separate the contribution of background fluorescence in the Raman spectrum. An ex vivo study of human coronary specimens also demonstrated that a tissue layer of 300 μm attenuates the Raman cholesterol signals by 50% at 850 nm excitation, which indicates that a lipid core up to 1 to 1.5 mm from the lumen could still be detected with this technique. Accordingly, the first in vivo application of catheter-based intravascular Raman spectroscopy was demonstrated by Buschman et al. This experimental study showed that the in vivo intravascular Raman signal obtained from an aorta was a simple summation of signal contributions of the vessel wall and blood. Several groups subsequently confirmed the feasibility of intravascular Raman spectroscopy for tissue characterization.

MRI-Based Approaches
An early study using a 5F receiver coil with a 1.5-T scanner investigated thoracic human aortas obtained at autopsy. The IV-MRI showed an agreement of 80% with histopathology for intimal thickness, 75% for fibrous cap grading, and 74% for necrotic core grading. Another study with heritable hyperlipidemic rabbits demonstrated the feasibility of IV-MRI to evaluate atherosclerotic plaque progression. The MRI was performed with a single-loop copper wire coil integrated in a 5F balloon catheter and a 1.5-T scanner. A good correlation was observed between the histological American Heart Association plaque characterization and MRI classifications, with an overall agreement of 88%. More recently, a study of human carotid endarterectomy specimens demonstrated that a standard 0.5-T scanner could still achieve a reasonable degree of resolution (156×250 μm) with a 5F IV-MRI coil. That study also suggested that various pulse sequences (magnetization transfer contrast, inversion recovery, and gradient echo sequences) may provide an efficient method of MRI plaque characterization.

Despite the lower in-plane resolution than with the larger receiver coils, a 0.030-in wire-based device has also been shown to be capable of accurate quantification and characterization of plaque. Using human aortoiliac arteries ex vivo, Larose et al. developed a tissue score equation for reasonable plaque characterization. Compared with IVUS in human iliac arteries in vivo, IV-MRI readily visualized inner and outer plaque boundaries even in lesions with extensive calcification that barred IVUS interpretation.

The self-contained IV-MRI device measures diffusion coefficients of atherosclerotic plaque components to determine the extent and location of increased vascular lipid infiltration. In a human autopsy study of aortic and coronary arteries, IV-MRI correlated with the histological diagnosis, resulting in 100% sensitivity and 89% specificity. Given the favorable safety and feasibility results in a pilot study, a larger multicenter clinical trial has been initiated to compare IV-MRI findings with biomarkers, IVUS, and clinical follow-up results.

Functional Evaluation of Biomechanical Plaque Properties
Elastography/Palpography
IVUS elastography that measures mechanical strain of the arterial wall is an extension of radiofrequency signal analysis. Local tissue deformation is determined by cross-correlation analysis of the radiofrequency signals recorded at 2 different intravascular pressures during end diastole. The calculated local radial strain is displayed in a color-coded manner on the plaque area (elastography) or luminal boundary (palpography). An initial ex vivo study with diseased human coronary and femoral arteries revealed different mean strain values among fibrous, fibrofatty, and fatty plaque components. A subsequent in vivo study with peripheral arteries of an atherosclerotic miniswine model demonstrated high sensitivity to identify fatty plaque material due to its increased mean strain value. The study also suggested that the presence of high-strain spots might indicate localized macrophage infiltration. These results were confirmed by a postmortem human coronary study, which demonstrated 88% sensitivity and 89% specificity to detect histological vulnerable plaque when it was defined as a high-strain region at the plaque surface with adjacent low-strain regions in elastography. In that study, the strain in caps also showed a high positive correlation with the amount of macrophages and an inverse relation to the amount of smooth muscle cells. One hypothesis is that active macrophage infiltration can cause local weakening of a fibrous cap by secretion of proteolytic enzymes. Accordingly, a recent clinical study using 3D IVUS palpography showed that the number of highly deformable plaques correlated with both unstable clinical presentation and C-reactive protein levels. The prognostic value of this modality is being investigated in prospective multicenter studies.

Emerging Techniques
Several other techniques are currently being explored to improve the intravascular assessment of vessel wall biomechanics. One group is developing an IVUS-based new elasticity analysis, referred to as strain power imaging. This technique performs a 2-dimensional search of radiofrequency data in the radial and lateral directions to measure accurate radial strain distribution despite catheter and arterial motion induced by cardiac contractions. Strain power around the heartbeat frequency is then calculated from the power spectrum of the strain profiles over a single cardiac cycle, so that the obtained image is theoretically independent of the cardiac cycle. Other groups are actively working on optical approaches (OCT elastography) that may offer improved sensitivity due to higher resolution and contrast. Flow imaging
based on Doppler OCT is another emerging technique that would potentially allow assessment of blood velocity distribution for shear stress profiling of the vessel wall. In addition, plaque viscoelasticity measurement by laser speckle imaging has recently demonstrated the potential for tissue characterization and cap-thickness estimation.

Physiological Assessment of Plaque Activity

Vessel Wall Inflammation

Macrophage Infiltration

Macrophage quantification by OCT is a signal-processing technique based on the hypothesis that macrophage-infiltrated caps may have a higher heterogeneity of optical index of refraction, exhibiting stronger optical scattering with a higher signal variance than less-infiltrated fibrous caps. An ex vivo study of lipid-rich arterial segments showed a strong positive correlation between the normalized standard deviation of OCT signal intensity and histological fibrous cap macrophage density. An optimal range of thresholds yielded 100% sensitivity and specificity for identification of caps containing >10% CD68 staining.

The same group subsequently demonstrated the potential feasibility of in vivo macrophage quantification (Figure 10). In that clinical study, macrophage densities determined by OCT were significantly higher in unstable patients for both lipid-rich and fibrous plaques. Particularly in culprit lesions, surface macrophage infiltration was more strongly associated with unstable clinical presentation than was subsurface infiltration. Sites of plaque rupture also showed a greater density than nonruptured sites. Prospective clinical studies using this novel technique, with or without antiinflammatory pharmacological interventions, may help prove the classic hypothesis that vulnerable plaques with increased local inflammation predict future acute coronary events.

 Thermal Heterogeneity

The feasibility of intravascular thermography for the in vivo assessment of focal inflammation has been validated in a rabbit aortic model. In that study, the aortic segments of hypercholesterolemic rabbits showed significant heterogeneity that was associated with increased plaque thickness by IVUS. After 3 months of dietary cholesterol lowering, however, this heterogeneity decreased significantly, whereas plaque thickness remained unchanged. The reduced temperature heterogeneity paralleled the changes in plaque histology, which showed a marked loss of macrophages.

The first clinical study with intravascular thermography reported that the temperature difference between atherosclerotic plaques and adjacent healthy segments increased progressively from control subjects to patients with stable angina, unstable angina, and acute myocardial infarction. The same group subsequently reported significant positive correlations of the temperature difference with multiple systemic markers of potential plaque vulnerability. A recent clinical study demonstrated a direct correlation of in vivo temperature data with corresponding histopathology of coronary atherectomy specimens.

Increased plaque temperature may also have an effect on clinical outcomes of percutaneous interventions. Other studies showed that the administration of statins was associated with decreased heterogeneity in patients with coronary artery disease, possibly suggesting a direct antiinflammatory effect of the statins. The clinical impact of these findings remains to be investigated in larger clinical studies.

Tissue pH

There has been an interesting attempt to use diffuse reflectance NIR spectroscopy for in situ measurement of tissue pH or lactate concentration in atherosclerotic plaques. These metabolic parameters may indicate the activity of macrophages and other inflammatory cells, thus offering additional functional measures of plaque vulnerability. The feasibility of this technique has been demonstrated in an ex vivo study using human carotid endarterectomy specimens, and further technical refinements are awaited for clinical applications.

Plaque Perfusion and Neovascularization

Vasa Vasorum Imaging

For the past several decades, mounting evidence has linked neovascularization within the arterial wall (proliferation of the vasa vasorum) to the development of atherosclerosis, as well as plaque vulnerability due to intraplaque hemorrhage and inflammation. Several animal studies have also shown that suppression of plaque neovascularization with angiogenesis inhibitors or statins can attenuate the progression of atherosclerosis. These pioneering works, however, were reported with histopathology, in vitro microcomputed tomography imaging, and clinical applications.
raphy, or preclinical targeted magnetic resonance. Recently, contrast-enhanced IVUS with microbubble agents has been proposed for in vivo quantification of vasa vasorum density and plaque perfusion. A preliminary human study using conventional IVUS systems with a clinically available contrast agent demonstrated the feasibility of tracking the distribution of and dynamic changes in echo density within the coronary plaque and adventitial region after intracoronary microbubble injection.81

One technical challenge is the detection and monitoring of relatively weak contrast signals on the background vessel wall structure. The above initial study relied on the digital processing of gray-scale, phase-correlated IVUS images. Therefore, the analysis was restricted to a single imaging plane, with the assumption that images acquired at the same point of successive cardiac cycles were not affected by tissue motion. Accordingly, the application of harmonic contrast imaging, a well-established technique for microvascular flow detection by lower-frequency ultrasonography, has been proposed recently (Figure 11).82 Second-harmonic imaging stimulates substantial bubble vibrations to emit energy at twice the transmitted frequency, thus generating images with a second-harmonic frequency band (eg, transmitting at 20 MHz and receiving at 40 MHz) in which the amplitudes of bubble echo are greater than those of tissue echo. This technique may also facilitate in vivo molecular imaging with targeted contrast microbubbles as assessed by IVUS.

**Molecular Imaging With Targeted Agents**

The utility of intravascular imaging can be enhanced significantly by the introduction of targeted contrast agents to specific tissue components, cells, molecules, or biological processes. This biomedical imaging technique, so-called molecular imaging, also enables site-targeted delivery of therapeutic agents with visual verification and quantification of the treatment (eg, microbubbles carrying therapeutic agents can be forced to explode, thus releasing drugs locally). In contrast to passive targeting that primarily utilizes nonspecific uptake of particles by macrophages, active targeting agents provide site-specific enhancement with a variety of ligands, including antibodies, peptides, polysaccharides, and aptamers, conjugated to the particle surface. A number of targets are being investigated, including adhesion molecules (eg, intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and selectins), thrombus (eg, fibrin, fibrinogen, integrin α₅β₃, and factor XIIIa), tissue factor, matrix metalloproteinases, and angiogenesis/neovascularization within the vessel wall.

Ultrasound applications traditionally utilize microbubble-based techniques, whereas nongaseous, acoustically reflective nanoparticles have also shown significant potential owing to their smaller particle sizes and greater in vivo stability.83,84 In a canine study using biotinylated, lipid-coated, perfluorocarbon emulsion nanoparticles, Lanza et al85 first demonstrated marked acoustic enhancement of in vivo thrombi. A more recent animal study with targeted nanoemulsion to tissue factor confirmed that acoustic nanoparticles can infiltrate arterial walls after balloon injury, detecting localized expression of overstretch-induced tissue factor with conventional IVUS.86 Several other groups have developed targeted echogenic liposomes and have proven the in vivo feasibility of IVUS to detect and quantify the various cell-surface molecular signatures of endothelium and atheroma components.84,87 Furthermore, extended efforts are ongoing...
to integrate therapeutic agents, such as antiproliferative drugs and gene transfection agents, into these ligand-targeted ultrasound contrast systems.\(^8\)

Similarly, several tissue/biology-specific MRI contrast agents are currently under development that can be created by attaching an affinity ligand to a magnetic compound, such as nanoparticles with gadolinium chelates or superparamagnetic particles of iron oxide (SPIOs). Finally, in vivo imaging of enzymatic activities has considerable clinical and scientific potential, because several families of proteases play crucial roles in both the progression and complications of atherosclerosis. For instance, cathepsins produced by macrophages, endothelial cells, or smooth muscle cells can degrade extracellular matrix and may therefore contribute to vascular remodeling or plaque destabilization. Recently, optical imaging agents that become brightly fluorescent after enzymatic cleavage by cathepsins have been developed for the detection of inflamed plaques (Figure 12).\(^9\) Compared with conventional antibody-based methods, this technology has a theoretical advantage to distinguish active enzymes from inactive zymogen precursors. In concert with the intravascular NIR fluorescence imaging system currently being developed, these protease-activated fluorescence sensors may enable direct quantitative visualization of active inflammatory process within human coronary plaques in vivo.

**Summary**

Recent advancements in noninvasive cardiovascular imaging now allow rapid and detailed visualization of cardiovascular structures. However, the clinical demand for catheter-based imaging is also growing, largely driven by evolving percutaneous treatment technologies that require precise procedural guidance or real-time assessment of treatment effects. These technologies include not only a variety of coronary interventions but also percutaneous treatment devices for structural heart disease or heart failure. As illustrated by late thrombosis of DES, the consequences of new treatments may also lead to a need for in-depth examination of the treated sites. Furthermore, a desire to identify vulnerable plaques has significantly stimulated the technological advancement of intravascular imaging beyond the provision of anatomic images. Although an ultimate goal in cardiology is to use systemic treatments to prevent vulnerable patients from experiencing adverse events, operators will continue to face the need to determine whether an existing lesion is at imminent risk of an acute event and thus calls for intensive local stabilization. Motivated by these expectations, active efforts are ongoing to develop a variety of advanced technologies to overcome the limitations of current intravascular imaging techniques. Although the majority of these new technologies are yet to mature, the advances in diagnostic modalities will enable us to better understand pathophysiology and will pave the way for new treatment strategies for patients. Finally, the clinical utility of intravascular imaging will be enhanced significantly when combined with treatment modalities that include catheter-based devices or hybrid molecular imaging/therapeutic agents.

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**Disclosures**

Dr Fitzgerald serves as a consultant/advisory board member of Cardio-Optics, Inc, Novadag Technologies, Inc, Volcano Therapeutics, Inc, and Prescient Medical, Inc. Dr Honda reports no conflicts.

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