Given the well-accepted limitations of coronary angiography, investigators and clinicians have had a strong interest in developing new approaches to defining the luminal encroachment, composition, and functional consequences of coronary atheromas. Intracoronary imaging techniques such as intravascular ultrasound (IVUS) were the initial techniques applied for this purpose (1). The validation of fractional flow reserve (FFR) as a measure of the functional significance of intermediate coronary stenoses has also provided an important advance in our ability to determine appropriate application of percutaneous coronary intervention (PCI) (2). More recently, advanced imaging techniques, such as virtual histology-intravascular ultrasound (VH-IVUS) to define high-risk plaques and necrotic cores by their ultrasound characteristics, and near infrared spectroscopy (NIRS) to detect lipid-rich plaques by their cholesterol ester composition, have also been developed. Despite these advances, limitations have continued in the evaluation of coronary atherosclerosis, and techniques such as angioscopy, palpography, shear stress imaging, and Raman and fluorescence spectroscopy are being actively studied (3). With its recent commercialization, optical coherence tomography (OCT) holds the potential to make significant contributions to this field.

Although the initial application of OCT to blood vessels by the Fujimoto group occurred in the mid-1990s (4), it has taken a number of years of development and validation to bring it to clinical use (3). OCT employs infrared light (invisible to the naked eye) to produce tomographic images, and has unprecedented resolution (10 to 15 μm) among intravascular imaging techniques. OCT is analogous to ultrasound B-mode imaging, but measures the intensity of reflected or backscattered light rather than acoustic waves. Light from the OCT is split, with a portion sent to the patient's artery and a portion to a reference arm, generating a reflected interference pattern that is analyzed for backscatter as a function of delay time to determine depth and transverse position. The intensity of the reflected light, which is dependent on the differences in refractive indices (backscatter and absorption) of the imaged tissue, is then displayed as an orange-red or grayscale image. Because plaque components have different intrinsic refractive indices (i.e., lipids have high attenuation and thus low penetration depth and cannot be seen as well, whereas calcium and collagen have low attenuation and high penetration depth), distinct patterns of composition can be generated. The penetration depth of infrared light wavelengths (1.3 μm) used in coronary OCT is approximately 0.1 to 2.0 mm. Because OCT is attenuated by blood before it reaches the vessel wall, the field of view must be flushed clear during imaging.

OCT imaging was initially performed using a time-domain algorithm that was limited by slow imaging speeds. This necessitated proximal balloon occlusion and flushing, leading to potential ischemia. The current OCT systems use a frequency-domain protocol that has rapid imaging speeds (20 mm/s) performed in conjunction with an optically transparent flush not requiring balloon occlusion. This important advance will allow widespread clinical application and reduced potential for complications (5).

A key question at this point is what information can be obtained from OCT that is not available with current techniques. For example, IVUS provides full vessel anatomical architecture; quantitates luminal compromise, extent of atheroma burden, inward or outward remodeling, stent dimensions, and malapposition; and has been validated in multiple clinical trials (1). However, IVUS has limitations in spatial resolution and plaque/thrombus characterization. VH-IVUS has been developed to further characterize atheroma components into calcified plaque, necrotic core,
fibrous, and fibro-fatty lesions. The PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) trial (6) demonstrated that IVUS-derived measures of plaque burden and VH-IVUS determination of thin-cap fibroatheromas (TCFA) were additive in predicting future cardiovascular events. Prospective clinical data with NIRS are not yet available, and comparisons of TCFA derived by VH-IVUS and necrotic cores detected by NIRS evaluation of cholesterol content would be of interest to assess whether these measures are complementary or redundant.

It is clear at this point that OCT provides high-resolution, well-defined images of intraluminal and endothelial/intimal structures such as ruptured plaques, thrombi, spontaneous dissections, and angiographically vague coronary anatomy, such as ostial, bifurcation, and left main lesions. It also is able to detect fibrous cap thickness and to identify TCFA (<75 μm), a key component of rupture-prone lesions. OCT is of value in determining stent parameters (edge dissections, expansion, apposition, neointima, stent coverage, and defining mechanisms of stent restenosis). Therefore, it will likely have a significant role, and perhaps become a preferred modality compared with IVUS, in facilitating the performance of PCI. However, due to its limited penetration and high attenuation by some plaque components, it remains to be seen whether it will ultimately discriminate lipid versus nonlipid components such as the necrotic cores that are associated with high potential for plaque rupture. It also cannot fully measure plaque burden, particularly in larger arteries, or adequately assess remodeling due to depth of penetration issues, and may not be as amenable to testing pharmacological therapeutic interventions as IVUS.

In this issue of the Journal, four reports provide initial insights into addressing the clinical potential of OCT. In the first study by Tearney et al. (7), a group of approximately 250 interested investigators and industry representatives developed a consensus report on proposed definitions, applications, and standards for the clinical use of OCT. The document, from a group of early developers and interested practitioners of the technique, defines their view of the state of the art. They provide a detailed overview of most aspects of OCT, including documentation of the level of evidence currently available supporting clinical applications. Although this group is not sanctioned under the aegis of any official organization, it will likely serve as the beginning of a broad discussion and roadmap for performing, analyzing, and reporting future studies related to OCT. However, several gaps of knowledge remain: 1) most of the data come from small studies and largely descriptive datasets; 2) limitations in imaging the vessel wall related to the procedure and generation of imaging artifacts will likely become more apparent as more experience is obtained; 3) the OCT evidence base on plaque composition will need to be supported by future studies; and 4) committees with broader interests should ultimately provide guidelines to define the usefulness of the individual imaging technologies as the evidence base increases.

The three other reports in this issue show the potential clinical utility of OCT. Alfonso et al. (8) demonstrate that OCT may detect angiographically occult spontaneous coronary dissections in patients that have nonatherosclerotic cardiovascular disease and that this knowledge changes clinical care. Gonzalo et al. (9) performed a comparison of OCT and FFR in intermediate lesions and showed that although OCT-derived measures of plaque of minimal lumen diameter appeared to be slightly better than FFR in defining functional significance, the difference was quite small and did not appear to be clinically significant due to low specificity. Finally, Kostis and Jang (10) demonstrated that acute in-lab stent thrombosis could be clearly observed to resolve by OCT within 24 h in response to antiplatelet therapy.

When viewing OCT images, one is struck by the exquisite detail and resolution of the technique, particularly in defining endothelial or vessel lumen/near field–based structures. However, although such previously unseen beautiful images of the coronary vasculature are nice to look at, the usefulness of this technique will ultimately rest on its ability to accurately identify the structures visualized. Importantly, the images must also result in improved clinical outcomes; for example, they should enhance stent deployment, prediction of late stent outcomes, and overall success of PCI. However, predicting future cardiovascular events in native lesions is a daunting task and perhaps a bit too much to ask for a stand-alone anatomically based technique. Advances in complementary imaging techniques, such as molecular imaging of pro-inflammatory components including macrophages and their byproducts and of oxidized lipids, which make up a large component of the necrotic core (11), may ultimately provide a more comprehensive assessment of risk. They may also guide targeting of focal and systemic therapies if further validated in clinical studies (12). For example, targeting oxidation-specific epitopes in high-risk lesions can be seen as an example of a “biotheranostic” approach; monoclonal antibodies can detect OSE in plasma using in vitro assays. When OSE biomarkers and other biomarkers are elevated, antibody-based magnetic resonance nanoparticles may be used to image them in the vessel wall. Finally, when detected at specific vascular sites, these oxidation-specific epitopes may be treated with a larger dose of the same antibody. This biotheranostic paradigm has been developed in our laboratory over the last 10 years using murine and human oxidation-specific antibodies (13–15).

To define the ultimate clinical utility of OCT, standards will need to be defined prospectively and linked to outcomes with appropriate studies. Undoubtedly, OCT will have an important niche in specific clinical situations where current imaging techniques have limitations. As we go forward, defining the optimal utility of OCT will provide a fertile and exciting opportunity for clinical investigation.
REFERENCES


Key Words: atherosclerosis • consensus document • coronary artery • optical coherence tomography • optical imaging.