Use of Optical Coherence Tomography for Accurate Characterization of Atherosclerosis

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Summary

Optical coherence tomography (OCT) is a novel imaging technology based on low-coherence interferometry that uses scattering of near-infrared light as a signal source to provide vascular cross-sectional imaging with definition far superior to any other available modality. With spatial resolution of up to 10μm, OCT provides 20-fold higher resolution than intravascular ultrasound (IVUS), currently the most used modality for intra-coronary imaging. OCT has the capacity to provide invaluable insight into the various phases of atherosclerotic disease and vascular response to therapeutics. Studies have shown the ability of OCT to detect arterial structures and assist in the determination of different histological constituents. Its capacity to distinguish different grades of atherosclerotic changes and the various types of plaques, as compared to histology, has recently been demonstrated with acceptable intra-observer and inter-observer correlations for these findings.

OCT provides unrivaled real-time *in vivo* endovascular resolution, which has been exploited to assess the vascular structures and response to device deployment. While depth remains a limitation for OCT plaque characterization beyond 2-mm, near-histological resolution can be achieved within the first millimeter of the vessel wall allowing unique assessment of fibrous cap characteristics and thickness. In addition, assessment of neointimal coverage, para-strut tissue patterns and stent apposition can now be scrutinized for individual struts on the micron scale, the so-called strut-level analysis.

OCT has propelled intravascular imaging into micron-level *in vivo* vascular analysis and is expected to soon become a valuable and indispensable tool for the cardiologists on both clinical and research applications.

Key Words

Optical coherence tomography, atherosclerosis, intravascular imaging

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Manuscript received October 20, 2008; revised manuscript received October 31, 2008; accepted October 31, 2008.

Introduction

Optical coherence tomography (OCT) is a novel optical imaging technology that provides cross-sectional tomographic imaging for biomedical structure with definition far superior to any other currently available modality[1]. The resolution capacity of OCT is due to the use of near-infrared light as its signal source. Biologic tissues have limited absorption of this light frequency and reflect or backscatter this energy. Utilizing these properties, OCT is able to obtain spatial resolution of up to 10μm, at least 10-fold that of intravascular ultrasound (IVUS)[2-5]. This increased resolution, however, comes at the expense of tissue penetration. The absorption and scattering of light by biological tissues limits OCT to a depth of $\leq$ 2mm in endovascular tissue[6]. However, the enhanced resolution allows accurate depiction of vascular components smaller than the resolution capacity of IVUS, for example thin-capped atheroma. Studies have validated the ability of OCT to accurately identify and differentiate atherosclerotic components. Beyond research applications, OCT will likely play a major role in routine interventional practice, as it provides a clear distinction between lumen and vessel wall interface, which is not always achieved with IVUS. Endovascular imaging in daily clinical practice is essentially based on lumen cross-sectional dimensions to guide both indication and results of percutaneous interventions. In this article, we aim to briefly describe the technical aspects of OCT image acquisition, summarize data on the use of OCT in atherosclerosis and coronary artery imaging, and present novel uses of OCT in therapeutic modalities.

OCT image acquisition

The current, commercially available catheter consists of a single-mode optical fiber in a hollow rotating or translating cable that emits and scans the OCT beam radially from the catheter axis (time domain OCT).[6] The diameter of the wire with transducer is as small as 0.014 inches. The probe terminates in an optical fiber, which is enclosed in a transparent plastic housing. Light is emitted radially to the endovascular tissue. A portion of the light is reflected from vascular structures and returns to the wire, which also receives this signal. The backscattered signal is analyzed for both the intensity of the returning signal, as well as time-of-flight, as it returns from the sample. As the wire is rotated, it acquires a continuous stream of information.

An attached computer processes the information obtained and renders a cross-sectional frame, or optical biopsy of the vessel. Wire pull-back is performed mechanically, which enables longitudinal assessment of the target vessel. Current pull-back speeds of 1mm/sec provide approximately 15 to 30 cross-sectional frames per mm. One major procedural limitation of intravascular OCT is the need to displace blood during imaging, because of signal attenuation caused by red blood cells. Currently, this displacement is accomplished by an over-the-wire low pressure, proximal balloon occlusion and flushing with either lactated Ringer's or normal saline during the pullback. The current OCT system consists of an optical fiber, a proximal low-pressure occlusion balloon catheter (Helios™Goodman, Advantec Vascular Corp™ Sunnyvale, CA, USA) and an OCT system mobile cart containing the optical imaging engine and computer for signal acquisition, analysis and image reconstruction (M2CV OCT Imaging System, LightLab, Westford, MA, USA). Study results demonstrated the safety of this system, with procedural success rates higher than IVUS[2]. However, careful patient selection is critical for safe and adequate image acquisition. Vessels suitable for OCT scan are normally between 2.5 and 3.75 mm in diameter, without excessive tortuosity (< 90° bend), without visible collaterals and with sufficient length of non-diseased proximal segment for balloon inflation.

New generation OCT systems are based on optical frequency domain imaging (OFDI). Individual spectral components of low coherence light are detected separately, which improves significantly signal-to-noise ratio compared to the current available "time-domain" OCT. Using flexible, narrow-diameter catheters, images with 500 radial A-lines per frame are acquired at a rate of approximately 100 frames per second, which allows real-time image acquisition at pullback speed of 15mm/sec during very brief displacement of blood by single bolus infusion of saline, without the need for vessel occlusion. These new OCT systems will soon be available, although clinical validation remains to be demonstrated. The LightLab OFDI M4 system will start an FDA-clinical feasibility study soon, Volcano and Terumo also have OFDI OCT prototypes that have been used in humans during live case demonstrations at international meetings and are expected to become available in the future.

Evaluation of vascular atherosclerosis

The OCT image acquisition uses light with a central wavelength at about 1300nm, which produces, based on low-coherence interferometry, images with axial resolution of up to 10μm and lateral resolution up to 20μm. Similar to IVUS, *in vitro* and *in vivo* studies suggest that the high definition of OCT can enable the distinction of microscopic arterial structures and assist in determination of different histological constituents including lipid, calcium and fibrous tissue[2] (Figures 1-3). In a rabbit model of atherosclerosis, Zimarino et al[7] demonstrated in injured carotid arteries that OCT was capable of detecting histologic atherosclerotic changes classified beyond grade III (extracellular lipid pools), but not subtle changes (grades I and II)[7]. OCT has been shown to be highly sensitive and specific for characterizing different types of atherosclerotic plaques in human coronary arteries, with very acceptable inter-observer and intra-observer variability. Yabushita, et al[8], examining 357 arterial segments of 90 cadavers, demonstrated sensitivity of 79%, 95% and 90% and specificity of 97%, 97% and 92% for OCT detection of fibrous, fibrocalcific and lipid-rich plaques, respectively, compared to histological examination[2]. Additional OCT studies performed in 76 patients found that the intra-observer correlation coefficients for minimal lumen diameter and minimal lumen area were 0.999 and 0.999, with percent errors of 2.0 ± 1.1% and 2.5 ± 2.4%, respectively. Inter-observer correlation coefficients were 0.997 and 0.998, with percent errors of 2.7 ± 2.1% and 4.6 ± 6.8%, respectively[8].

With this background, investigators probed the ability of OCT to detect additional components of atherosclerosis. Previous investigation has shown that plaque rupture in acute coronary syndrome is often found at the shoulder of atheromatous plaques with a large lipid core and a thin fibrous cap, termed thin-capped fibrous atheroma (TCFA)[9]. It was determined that the cap thickness of TCFA associated with plaque rupture was under 65 micron[10], well under the resolution capacity of IVUS. Kume, et al[11] demonstrated the ability of OCT to accurately measure fibrous cap thickness as compared to histology. Further post-mortem studies showed a sensitivity of 92% and a specificity of 75% for OCT detection of TCFA as compared to histology[12].

The goal of intravascular imaging is not only to depict established disease, but also to detect early stages of disease in order to target those areas for therapeutic intervention. Previous studies identified the role of macrophage infiltration of atherosclerotic plaques and clinical events[9,13]. By identifying OCT signal variance, MacNeill et al[14] demonstrated greater macrophage density, both for fibrous and lipid-rich plaques in patients with unstable *versus* stable coronary artery disease. Further studies established a very significant correlation between OCT and histologic measurements of fibrous cap macrophage density[15].

Unabated atherosclerosis may lead to plaque rupture and introduction of vascular wall constituents to the bloodstream. The ability of an intravascular imaging modality to identify even small areas of thrombus can identify areas of tissue injury and once again highlight areas for therapeutic intervention. The capacity of OCT to detect intravascular thrombosis (Figure 4) was studied in rabbit models and showed good correlation with histological findings[16]. Seminal post-mortem investigation determining the diagnostic accuracy OCT to detect coronary thrombus showed the ability of OCT to identify and differentiate red and white thrombi[17]. In the early stages of thrombus formation, blood cell constituents are trapped within the rapidly organizing thrombus. As the thrombus matures and becomes more fibrous and less cellular, the thrombus turns from "red" to "white." This important distinction may aid in determining optimal therapeutic strategy. These impressive *in vitro* results should not be expected for *in vivo* imaging, because of blood, vessel tortuosity, position of the wire and motion

induced artifacts. Nevertheless, these validation studies provide strong scientific support for the unique properties of OCT technology, which represents a major advance in endovascular imaging.

OCT evaluation for percutaneous coronary interventions

The impact of minimal lumen diameter (MLA) on clinical outcomes in patients with contemporary percutaneous coronary intervention (PCI) has been extensively reported[18]. However, the measurement of lumen area by means of IVUS still needs considerable manual interpolation and might be unrealistic for some clinical situations. On the other hand, online automated contour detection algorithm (collaboration between University Hospitals Case Medical Center Core Laboratory, Cleveland, OH and LightLab Imaging Inc., Westford, MA) enables instantaneous delineation and measurements of lumen area with virtually no observer interference because of the clear difference in intensity between lumen and vessel wall depicted by OCT. The ability of OCT to delineate such interfaces permits less interpolation than with other clinically available imaging modalities. As such, reproducibility of measurements of MLA by OCT has been very good[19].

Although most of the coronary artery measurements show acceptable correlation between OCT and IVUS, some variables (minimal lumen diameter and MLA) seem to be underestimated by OCT. It has been proposed that this may be the result of lower intravascular pressure during image acquisition[2]. Alternatively, the larger diameter IVUS probe may artificially dilate the lumen while the smaller OCT wire may depict true luminal contour without distortion.

Evaluation of neointimal coverage and stent apposition

The power of OCT to provide unrivaled endovascular resolution has been exploited to assess the vascular response to device deployment. It is now possible to perform strut-level analysis, the evaluation of the vascular response at individual stent struts. Variables such as neointimal growth and stent apposition are now able to be scrutinized for individual struts on the micron scale. The correlation between this detailed assessment and clinical outcomes remains uncertain.

Because the light source of OCT cannot penetrate metal, caution is advised for the interpretation of individual stent struts, as the high intensity signal of the OCT image does not represent the morphology of the true strut. (Figure 5) Using the previously mentioned software, the thickness of the high intensity shadow representing a stent strut was determined. Thickness measurements of 2250 struts in 471 cross-sectional OCT images were obtained 6 months after Taxus Liberte stent implantation. Measurements were determined along the vector, of which initial point was located at the centroid of the vessel. Interestingly, the mean measured thickness was 37±8 μm (20-70 μm) (Suzuki N, Costa MA; unpublished data), which is definitely smaller

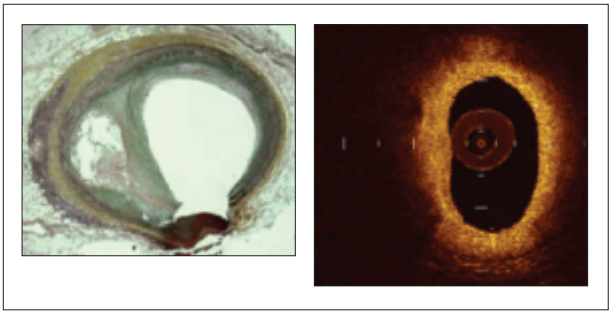


Figure 1 - Lipid-rich plaque, which is characterized by a diffuse poor signal structure. The borders are irregular and not well delineated. Courtesy of Chenyang Xu and Joseph Schmitt, LightLab Imaging, Inc., Westford, MA.

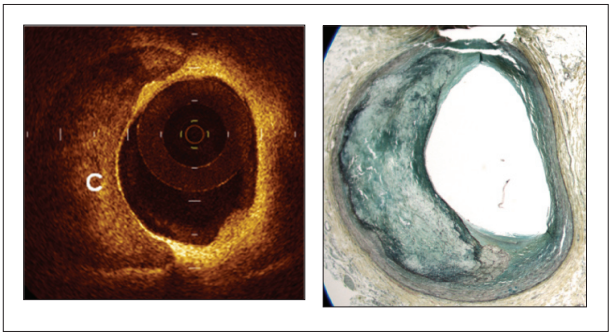


Figure 2 - Calcified plaque characterized by well delineated borders, surrounding a poor focal signal region. Courtesy of Chenyang Xu and Joseph Schmitt, LightLab Imaging, Inc., Westford, MA.

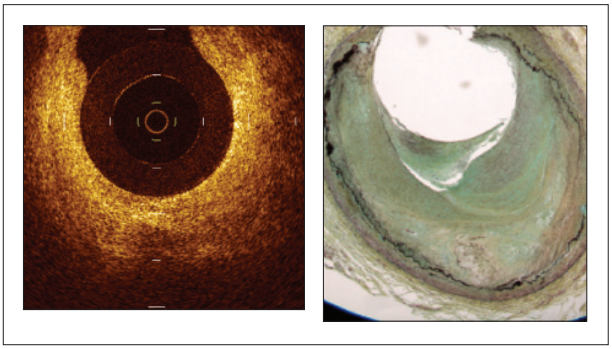


Figure 3 - Fibrotic plaque, defined as high-intensity homogeneous tissue. Courtesy of Chenyang Xu and Joseph Schmitt, LightLab Imaging, Inc., Westford, MA.

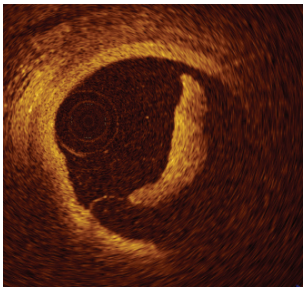
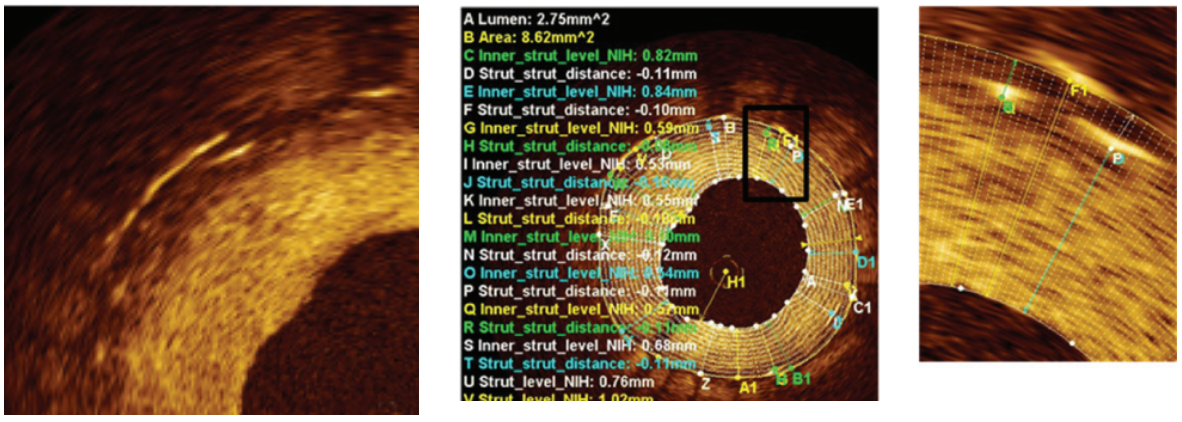


Figure 4 - The thrombus produces a signal-rich structure with backscattering on OCT. In this particular case, most of the thrombus is floating with minimal attachment to the vessel wall.

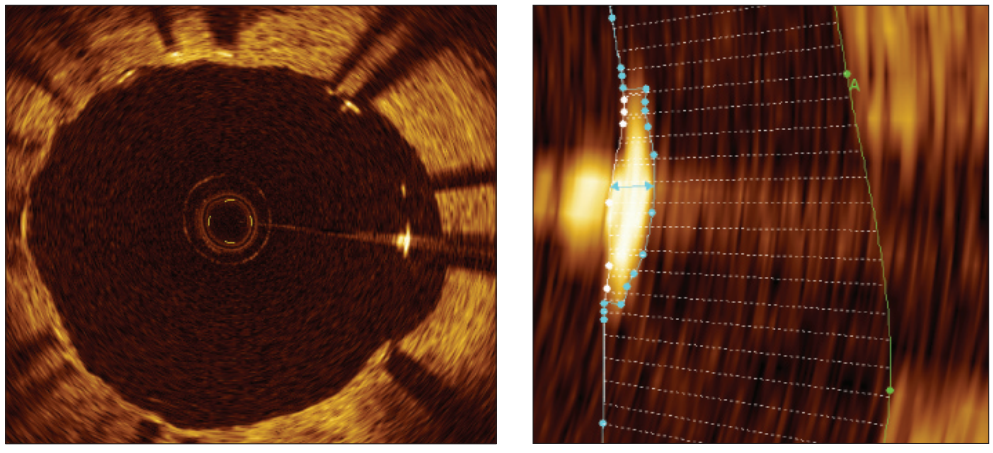
than the actual strut thickness (97 μm). This inadequate strut thickness has been observed by others[20]. Therefore, the high intensity structure cannot represent the strut thickness, but is rather a reflection of the strut surface. This highlights the need for standardized data interpretation and reporting strategies.

Recent data suggest that malapposition and uncovered struts rates are as high as 6% (Figure 5) and 15%, respectively, after drug-eluting stent (DES) implantation, higher than bare-metal stents (BMS): 0.1% and 1% respectively, in a three-month follow-up, mostly in bifurcation and overlapping segments[21,22]. Furthermore, 2 years after stent implantation, the frequency of struts that remained without endothelization were higher in the DES group. The belief that strut coverage by OCT is a marker of endothelization is a gross extrapolation; the endothelium is a microscopic single cell layer that is clinically "invisible", even for the best image modality, such as the OCT. In addition, diseased coronary segments, even prior to intervention, are denuded of or have dysfunctional endothelium. Regardless of the presence or absence of a functional endothelium, it has been proposed that a ratio of uncovered struts to total struts per cross-sectional OCT image



A

Figure 5A - Cross-sectional image of an overlapping region with lumen area of 2.75 mm² and external stent contour of 8.62 mm². Strut level analysis reveals different thickness of neointimal. The strut-to-strut distance is also calculated (detail). The 360 cords allow a detailed analysis of the neointimal distribution. Cardiovascular Imaging Core Laboratory, Harrington McLaughlin Heart and Vascular Institute, University Hospitals Case Medical Center, Cleveland - Ohio.



B

Figure 5B - Cross-sectional image revealing a region of strut malapposition. At least two struts are involved. Applying the 360 cords, the distance between the blooming of the strut (blue) and the vessel wall can be automatically calculated and the malapposed struts identified. In this particular case, the average distance was 300 μm, which is more than twice the average strut thickness. Cardiovascular Imaging Core Laboratory, Harrington McLaughlin Heart and Vascular Institute, University Hospitals Case Medical Center, Cleveland - Ohio.

can predict those patients at risk for late stent thrombosis[21,23,-25]. This, and many other interesting hypotheses, illustrates the potential wealth of information which can now be gleaned by utilizing OCT for intravascular imaging.

Acknowledgements

Special thanks to LightLab Imaging, LLC for supplying images for this article and for their continuous support and collaboration with the Harrington McLaughlin Heart and Vascular Institute, University Hospitals Case Medical Center, Cleveland, Ohio.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any post-graduation program.

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