Ex Vivo Imaging of Chronic Total Occlusions Using Forward-Looking Optical Coherence Tomography

Nigel R. Munce, MSc,[1]* Victor X.D. Yang, MD, PhD,[1,2,5] Beau A. Standish,[1] Beiping Qiang, MD, PhD,[3]
Jagdish Butany, MD,[6] Brian K. Courtney, MD,[4] John J. Graham, MD,[4,5] Alexander J. Dick, MD, FACC,[4,5]
Bradley H. Strauss, MD, PhD, FACC,[3] Graham A. Wright, PhD,[1,5] and I. Alex Vitkin, PhD[1,2,7]

[1]Department of Medical Biophysics, University of Toronto, Toronto, Canada

[2]Division of Biophysics and Bioimaging, Ontario Cancer Institute, University of Toronto, Toronto, Canada

[3]Roy and Ann Foss Interventional Cardiology Research Program, Terrence Donelly Heart Centre,
St Michael's Hospital, University of Toronto, Toronto, Canada

[4]Division of Cardiology, Sunnybrook Health Science Centre, University of Toronto, Toronto, Canada

[5]Imaging Research Program, Sunnybrook Health Science Centre, University of Toronto, Toronto, Canada

[6]Department of Laboratory Medicine and Pathobiology; and Division of Pathology, University Health Network,
University of Toronto, Toronto, Canada

[7]Department of Radiation Oncology, University of Toronto, Toronto, Canada

Background and Objectives: Percutaneous coronary interventions (PCI) of chronic total occlusions (CTOs) of arteries are more challenging lesions to treat with angioplasty and stenting than stenotic vessels due primarily to the difficulty in guiding the wire across the lesion. Angiography alone is unable to differentiate between the occluded lumen and the vessel wall and to characterize the content of the occlusion. New technologies to aid in interventional guidance are therefore highly desirable. We sought to evaluate tissue characterization in arterial (CTOs) by imaging ex vivo peripheral arterial samples with optical coherence tomography (OCT).

Study Design/Materials and Methods: Ex vivo arterial samples were obtained from patients undergoing peripheral limb amputation. Samples were imaged in an en face orientation using an OCT system, enabling sequential acquisition of longitudinal images and volumetric reconstruction of cross-sectional views of the occluded arteries. Histology was performed for comparison.

Results: OCT imaging reliably differentiated between the occluded lumen and the underlying arterial wall in peripheral CTOs. OCT correctly identified tissue composition within the CTO, such as the presence of collagen and calcium and was also able to identify intraluminal microchannels.

Conclusions: OCT imaging of CTO anatomy and tissue characteristics may potentially lead to substantial improvements in PCI interventions by providing novel guiding capabilities. Lasers Surg. Med. 39:28–35, 2007.
© 2006 Wiley-Liss, Inc.

Key words: intravascular imaging; arterial disease; interventional cardiology; optical coherence tomography; chronic total occlusions

INTRODUCTION

Chronic total occlusions (CTO) of coronary and peripheral arteries are generally defined as occluded arteries of 3 months duration or longer [1]. Totally occluded arteries are observed in as many as one-third of all X-ray angiograms [2]. The observation of a CTO under X-ray angiography is the most common reason for referral to bypass surgery as opposed to minimally invasive percutaneous approaches [3]. Percutaneous interventions of coronary and peripheral artery CTOs have only limited success rates (approximately 75% in coronary lesions [4]) due to the inability of the operator to easily direct a guidewire through the occluded lumen without dissecting the adjacent arterial wall. A limited number of histological studies have shown that the occluded lumen of a CTO is a complex lesion containing variable amounts of collagen, lipids, calcification, and intraluminal microchannels [5,6]. The border between lumen and the underlying arterial wall cannot be visualized by contrast angiography, leading to the frequent occurrence of directing guidewires into a subintimal location and procedural failure, even possibly vessel perforation. Recently, we have suggested that intraluminal microchannels, 100–200 μm in diameter, which cannot be identified by current imaging techniques, may play a role in predicting the ease with which the occlusion can be crossed with a guidewire [7]. There is thus a need for investigating new imaging modalities to aid in characterization and guidance of intervention in CTOs.

Optical coherence tomography (OCT) is an imaging modality that uses the interference of light reflected back from the tissue with light from a reference arm to form an image based on the depth-resolved reflectivity of the sample, to a depth of approximately 2 mm in tissue [8]. OCT's axial resolution, on the order of $3-15$ μm, has been shown to enable differentiation of arterial layers [9] and identification of various arterial pathologies [10,11]. Contrast in OCT is provided by both the intrinsic back-scattering properties of the different tissue types, as well as reflections from the different layers. In the intravascular forward-looking geometry, more amenable to interventional guidance, tissue interfaces are likely to be at an acute angle to the imaging direction. Thus contrast is mostly derived from the reflective properties of the tissue itself.

Recently, an optical coherence reflectometry system, which utilized only single-line (one-dimensional) depth profiles of reflections from interfaces, was approved for use in CTOs. Initial studies suggested that this system was able to differentiate between deeper layers of the vessel wall and the occluded lumen [12−15]. However, this system does not provide images of vessel layer boundaries or identify tissue composition within each layer.

We have thus been examining the potential utility of a forward-looking OCT imaging geometry to provide detailed cross-sectional images of the arterial wall and reliably differentiate tissue layers and identify specific tissue composition. We now report on our first ex-vivo experience with OCT imaging of human peripheral CTOs.

MATERIALS AND METHODS

Sample Preparation

Twenty-two samples of peripheral CTOs were obtained from below knee amputated limbs from 14 patients with peripheral artery disease, with informed consent under protocols approved by the hospital research ethics committee. Angiograms were obtained prior to amputation to identify the area of occlusion. The diseased arteries were dissected out of the limbs following amputation and stored in phosphate-buffered saline at 4°C. The arteries were cut into 5-mm sections. The maximum time between amputation and imaging was 1 week.

OCT Imaging

Arterial samples were imaged using a previously described time-domain OCT system [16]. The geometry of the scanning is illustrated in Figure 1. OCT images are presented on a log-based gray scale with scale bars of 1 mm appearing in red in the figures. This system employs a broadband low coherence source with a polarized output of 18 mW at a center wavelength of 1.3 μm with a bandwidth of $\Delta\lambda = 63$ nm, yielding a coherence length (axial resolution) of $\sim$10 μm in tissue. The reference arm consists of a rapid scanning optical delay line and a phase modulator. The sample arm consists of a single-mode fiber capped with a ball-lens, mounted on a three-dimensional computer-controlled micro-positioning stage, yielding a spot size (lateral resolution) of $\sim$20 μm.

Samples were attached to a piece of Styrofoam in order to preserve their orientation for later histological analysis. The specimen was oriented with the vessel axis parallel to the imaging fiber in order to approximate a forward-viewing intravascular imaging geometry. Lateral scanning combined with coherence gate depth scanning yielded a two-dimensional subsurface longitudinally-oriented OCT image, acquired at a rate of one frame per second. The probe was then translated across the sample in the orthogonal lateral direction in 10 μm increments, to yield a series of approximately 300 adjacent longitudinal slices acquired in 5 minutes that were then used for three-dimensional reconstruction and visualization.

For off-line three-dimensional visualization and reconstruction, OCT images were downloaded into Amira Visualization software (Mercury Computer Systems, Berlin, Germany). This software was used to reconstruct perpendicular (cross sectional) views of the arterial sample, by converting the set of adjacent two-dimensional longitudinal images into a three dimensional volume which
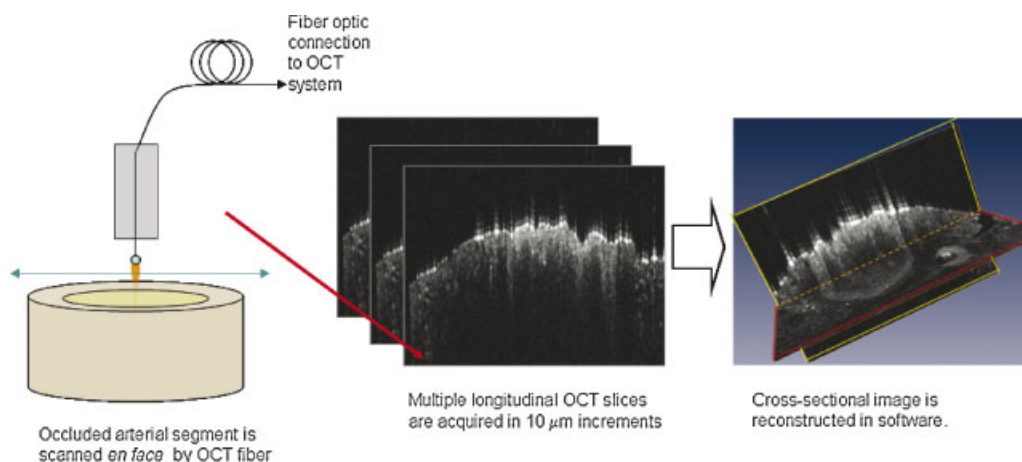

Fig. 1. Schematic of the OCT probe—Arterial sample arrangement used for OCT image acquisition. [Figure can be viewed in color online via www.interscience.wiley.com.]

could then be viewed in arbitrary orientations/projections. Reconstruction time was approximately 10 seconds. Brown lines are shown through each OCT image in the figures to indicate the location of the corresponding orthogonal slice.

Histology Processing

Immediately following OCT imaging, arterial samples were placed in formalin and sent for histology. A cross-sectional slice was first obtained and then the sample was re-embedded and sectioned longitudinally. Longitudinal sections were taken every 100 µm to ensure similar views in both histology and OCT imaging. Sections were stained with elastin trichrome to identify elastic tissue (black), muscle and blood (red), and collagen (blue). Calcification was identified with Von Kossa's stain as black. Lipid was identified with Oil Red O in frozen sections (showing lipid as red). Histology slides were scanned under a white light slide scanner (Aperio Technologies, Vista, CA) to allow for high resolution (20×) large field-of-view histology images.

RESULTS

CTOs obtained and scanned could be generalized into several principal types based on histological appearance:

1. Extensively calcified wall, dense collagen occupying the lumen ($n = 6$).
2. Microcalcifications within the lumen, embedded in collagen ($n = 6$).
3. Extensive smooth muscle cell infiltration with collagen in lumen ($n = 4$).
4. High lipid content in lumen ($n = 2$).
5. Dense collagen within lumen ($n = 4$).

In the OCT images, dense fibrotic tissue appeared bright, while highly cellular areas and looser connective tissue appeared darker. Such an occlusion is shown in Figure 2 where smooth muscle cells infiltrating the occluded lumen (OL) are seen as a dark region within the occlusion on the OCT images (Fig. 2a,b) and as a red stain within occluded lumen in the elastic trichrome histology (Fig. 2c,d). The muscular media in this case also appears as dark region (M) in both longitudinal (a) and reconstructed axial (b) OCT slices.

Figure 3 shows an occluded artery with an occluded lumen composed of mostly collagen that show up as uniformly scattering region under OCT (Fig. 3a,b). Moderate calcium deposits (C) within the media layers are seen under histology (Fig. 3c,d).

Figure 4 presents a very chronic, heavily calcified occlusion in which intramural calcification appeared as superficially reflective, signal poor regions within the arterial wall as shown in the region labeled C in the longitudinal OCT image in Figure 4a. Representative histology is shown in Figures 4c,d that illustrate large areas of "fallout" indicative of large pieces of calcium.

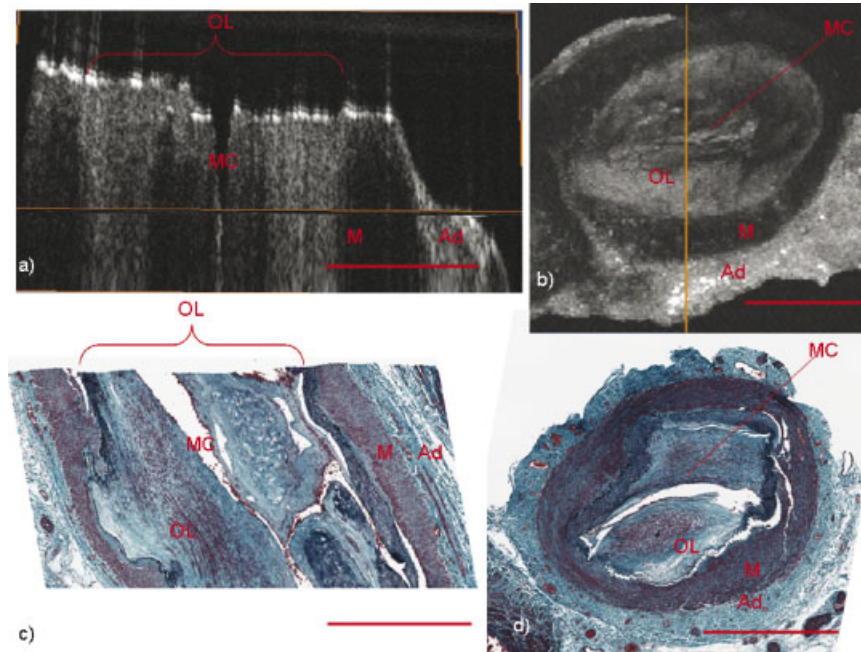An example of an occluded artery with extensive intraluminal microcalcifications embedded within the

Fig. 2. An angiographically-occluded artery is shown in both longitudinal (**a**) and reconstructed axial OCT images (**b**). Darker regions seen on OCT slices (a) and (b) within the occluded lumen (OL) represent infiltration of smooth muscle cells; while the brighter regions are seen as regions of fibrosis as evidenced by histology. A long, thin (100 by 1,000 µm) microchannel (MC) is identified within the lumen and is seen on both longitudinal and axial OCT images as well as histology. Medial and Adventitial layers are labeled M and Ad respectively. Histology is elastin trichrome. Bars = 1 mm. [Figure can be viewed in color online via www.interscience.wiley.com.]
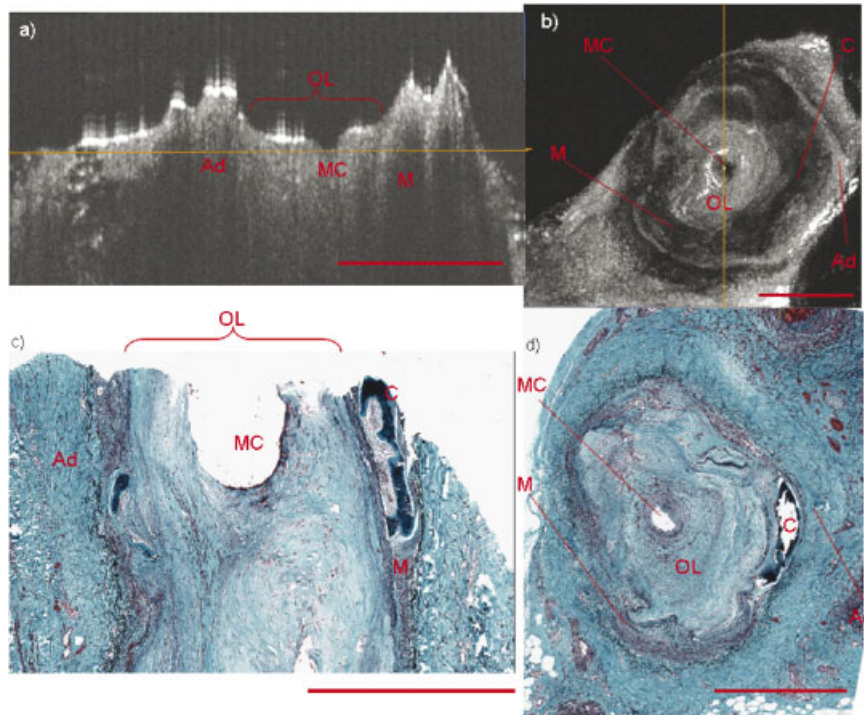
Fig. 3. An occlusion with moderate calcification (labeled C) within the medial layer (M). A small central microchannel (MC) within the occluded lumen (OL) is identified under both OCT (**a**, **b**) and histological sections (**c**, **d**). The adventitia (Ad) appears as a peripheral ring around the artery labeled in OCT axial image (b) and histology (d). Histology is elastin trichrome. Bars = 1 mm. [Figure can be viewed in color online via www.interscience.wiley.com.]

collagen matrix is shown in Figure 5. These microcalcifications were seen as highly reflective spots under OCT within the CTO that greatly attenuate the OCT signal with depth as shown in Figures 5a,d in the region labeled C.

A CTO with large lipid deposits is presented in Figure 6. Regions of lipids (L) were observed as signal poor spaces within the CTO as shown in OCT images in Figure 6a,b and confirmed using Oil Red stain shown in Figure 6c.

Intraluminal microchannels within the occlusion were identified in most OCT images as small crevices on the longitudinal slices and holes on the cross sectional slices; that were confirmed by histology. The appearance of the different potential components of CTOs under OCT is summarized in Table 1.

DISCUSSION

This is the first study to report on ex vivo imaging and characterization of CTOs using OCT. We have been able to use multiple longitudinal OCT slices to generate cross sectional images of occluded arteries. In all cases, these reconstructed axial views exhibited significantly more information than the original longitudinal slices. The calculated reconstructed cross sectional slices were crucial for reliably differentiating the arterial wall layers (occluded lumen, media, and adventitia) and identifying specific

tissue composition within the occluded lumen and the media.

Identification of the Vessel Wall

Due to its high collagen content, the occluded lumen of the vessels typically had a higher back-scattering signal than the surrounding medial layers allowing for identification of the occlusion. Cases in which the media appeared fibrotic and hence bright on OCT (as in Fig. 5a) still displayed small muscular regions that maintained a dark OCT signal. This variation in intensity from the media illustrates the necessity of imaging in order to identify the different arterial layers. Additionally, the advential layer could be identified in most cases, except those in which severe intramural calcification obscured the boundary between the media and adventitial layers as is seen in Figure 4.

Identification of Specific Tissue Characteristics

This is the first demonstration of OCT's capacity to visualize microchannels in CTOs. In all cases, endoluminal microchannels, greater than 50 μm in size, could be accurately identified within the occluded lumen by OCT on reconstructed axial slices. Initial imaging studies using μCT have shown the ability to perfuse these channels with
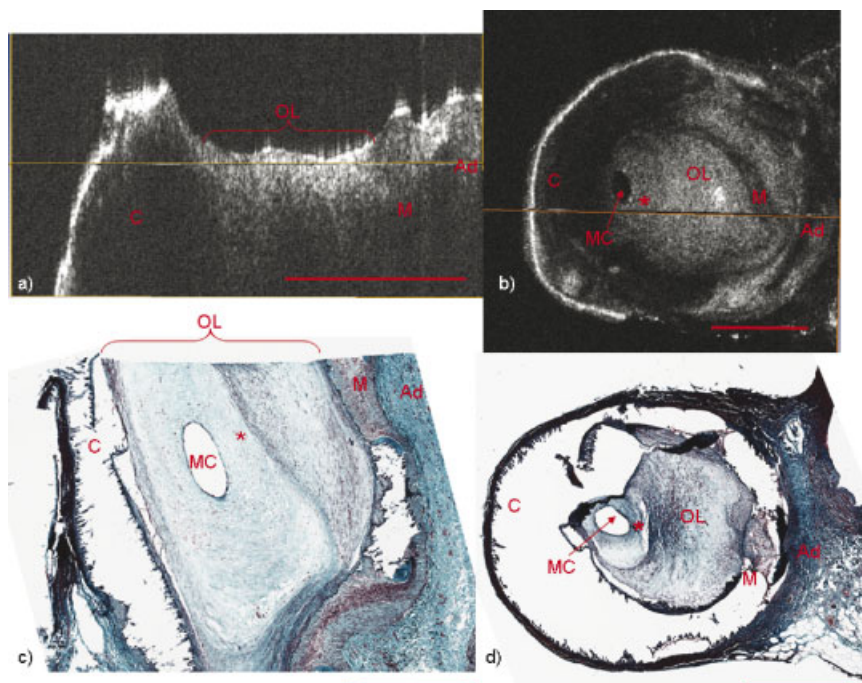
Fig. 4. Illustrates an occlusion with a small microchannel and extensive intramural calcification. Large calcium deposits, labeled C, present in the media (M) obscure differentiation between the different arterial layers on the individual OCT slices (**a**, **b**); however, the occluded lumen (OL) is easily identified as a brighter region within the centre of the artery. A microchannel, labeled MC, approximately 200 microns in diameter is identified within the occluded lumen on the axial slice. The asterisk in the axial OCT slice identifies a region of less dense collagen surrounding the microchannel. Again regions of collagen within the occluded lumen display extensive smooth muscle cell infiltration resulting in areas of different signal intensity within the occlusion. Histology is elastin trichrome. Bars = 1 mm. [Figure can be viewed in color online via www.interscience.wiley.com.]

radio-opaque casting polymers [7] suggesting that clearing these channels of blood with a saline flush, as would be required for in vivo imaging, is possible. In combination with clearing of the blood field in a CTO, microchannels may provide greater OCT imaging depth than one would normally expect if the occlusion were completely solid. This increase in depth range is an ideal application for new frequency-domain OCT systems that could provide up to 4 mm imaging through a clarified straight microchannel [17].

In this study, intramural calcification appeared as highly reflective regions within the wall of the artery with a signal poor region below it. This appearance is different to that reported in previous OCT arterial studies [10,11] using side-viewing OCT geometries that reported a clearly defined signal poor region. We attribute this difference to the segmental nature of the samples scanned in an en face geometry in this study as opposed to a side-viewing probe. In the side-viewing case, calcification is viewed through the intimal layer of the artery and therefore the reflection is not as pronounced as it is when viewing an air-calcium interface as presented here.

The OCT appearance of lipid, smooth muscle cell, fibrotic regions, and microcalcifications reported in this study agrees with previous reports on these components studied in vessel wall imaging [10,11,18]. The identification of lipid by OCT was, however, often obscured due to its co-localization with microcalcifications in the CTO.

Thrombus within or around the occlusion was occasionally seen as a bright signal lining the microchannel(s) of the CTO. Studies by others [19] suggest OCT's ability to identify and differentiate between red and white thrombus within the coronary arteries. Whether OCT can be used to determine the extent of organization within thrombus remains, however, a subject of future work.

Significance of Imaging CTOs for Tissue Boundaries and Specific Tissue Composition

Advanced CTO imaging techniques that are additive to contrast angiography remain a highly desired but unrealized goal. Success rates in CTOs, both peripheral and coronary, are much lower than stenotic but non-fully occluded lesions, in part due to inadequate visualization of the occluded segment. Additionally, the lack of imaging modalities capable of discerning the composition of total occlusions has resulted in a poor understanding of the role of each specific tissue component in procedural success or failure. For example, several studies have offered differing views on the role of calcification as an adverse predictive factor for successful CTO recanalization [20,21]. However,
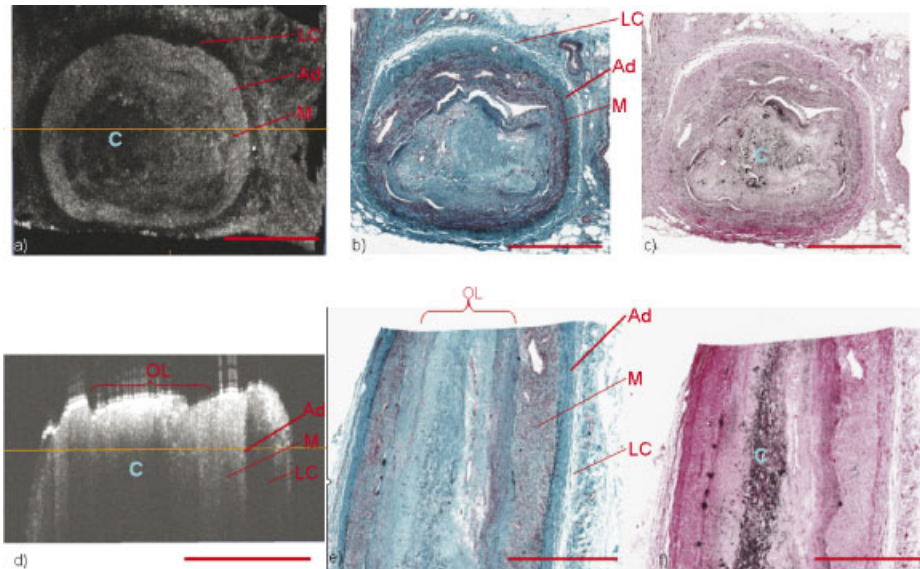
Fig. 5. OCT images of a CTO with lumenal micro-calcifications, labeled C, are shown in (**a**) and (**d**). The lumen appears histologically occluded save for the presence of several small (∼50 μm) holes that are not seen under OCT (**b**). Van Kossa's staining (**c**) and (**f**) indicates calcium deposits within the collagen matrix of the occluded lumen and suggesting that these holes are mostly calcium. These deposits are seen as highly reflective dots to a depth of 300 μm under OCT (d). Collagen-rich areas appear as bright, regions to a depth of 1 mm as before. In this case, it is difficult to distinguish the media from the adventitia due to fibrosis of the medial layer resulting in a high backscattered signal from inner regions of the media. Outer portions of the media (M), however, maintain their dense muscular structure and are seen as a thin dark region identified in (a). Loose connective (LC) tissue surrounding the artery is seen as a dark band surrounding the artery. Histology is elastin trichrome (b) and (e) and Van Kossa's Stain (c) and (f). Bars = 1 mm. [Figure can be viewed in color online via www.interscience.wiley.com.]

contrast angiography is limited in identifying intramural calcifications and their precise location within the wall. It is likely that calcification restricted to deep arterial wall layers will have a different effect than intraluminal calcifications. Other components of CTOs, particularly collagen, smooth muscle cells and lipid, which can currently only be assessed through histological means, may also portend different success rates. New therapies, such as enzyme-mediated collagen degradation [22], may be better-suited for specific lesion pathologies that cannot be currently identified nor differentiated by contrast angiography but are within the diagnostic ability of OCT. Recently, we have also suggested that intraluminal microchannels are an important predictor of lesion crossing and a potential target for angiogenic CTO therapies [7]. The identification of these microchannels by imaging modalities such as OCT could help clinicians select favorable CTOs for treatment, guide therapy during percutaneous interventions, and also assess the effects of angiogenic therapeutic approaches. Conversely, large lipid deposits may identify more complex CTOs with high likelihood of distal embolization. Thus, the identification of these lipid deposits within the CTO could alter the decision to attempt therapy on a CTO to avoid this risk or potentially allow the interventionalist to try to avoid the large lipid core. While more work is required to identify OCT's sensitivity and specificity in identifying these pathological features, this study suggests that OCT's ability to provide a detailed subsurface image of an occluded artery may identify an optimal interventional path and assess the variation in the arterial wall integrity across a large region of the artery.

In Vivo Implementation

Practical in vivo intravascular forward-viewing OCT imaging will require several improvements to the probe design used here. The probe must be flexible and self contained (no exposed moving parts) with a diameter of 2 mm or less in order to facilitate access to the coronary arteries. Forward-viewing OCT probes [23–26], typically have long rigid segments (> 2 cm) at the distal end that would be unsuitable for use within tortuous vasculature. The probe must also image a wide viewing area in order to visualize the entire occlusion. Designs involving scanning a fiber optic across a GRIN lens would be amenable to such requirements; however miniaturization of such probes remains an ongoing research area. In order to obtain three dimensional images in vivo, similar to the ones presented here, in vivo, such scanning probes could be simultaneously rotated using a torque cable. Frequency domain OCT systems comparable to those reported in the literature [27], would be required to ensure clinically acceptable volumetric imaging times on the order of a second or less. Such high frame-rate systems may permit imaging within the time window created by a saline flush alone, without the
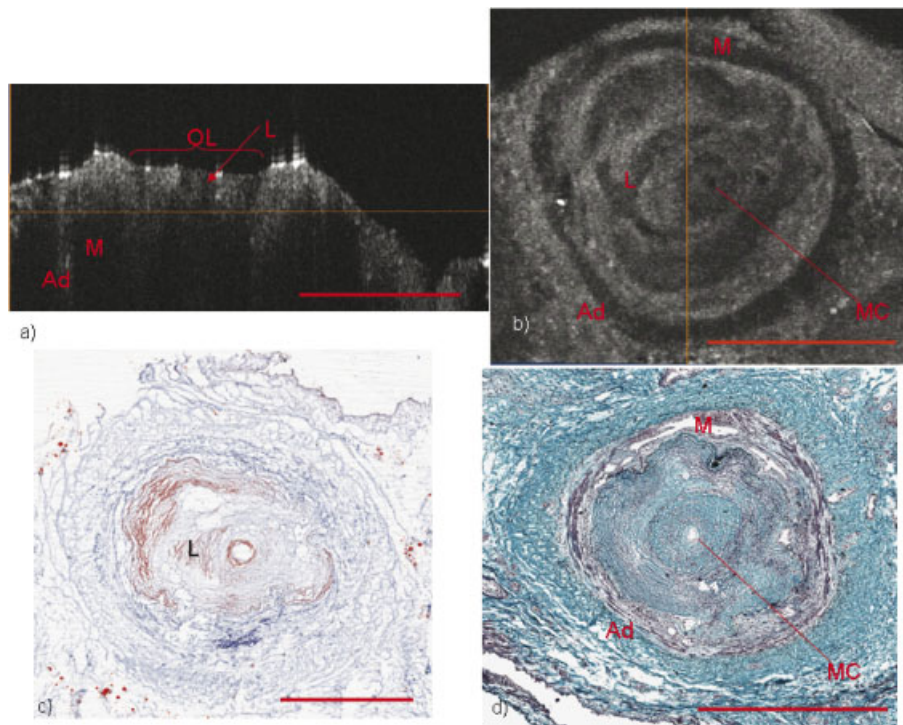
Fig. 6. OCT images of an occluded anterior tibial artery demonstrating high lipid content are shown in (**a**) and (**b**). A small central microchannel (MC) is seen in both reconstructed cross sectional OCT slices and histology. Lipid deposition, labeled L, is seen both within the collagen matrix of the CTO as well as accumulation around the central microchannel on the Oil Red O histology shown in (**c**). These regions are seen as weakly scattering regions in the OCT images. Lipid deposition around the central microchannel appears as small segmental deposits seen in the longitudinal OCT image shown in (a). Areas of the lumen containing a high collagen content once again appear as bright under the OCT images. Histology is Oil Red O in (c) and Elastin Trichrome (d). Bars = 1 mm. [Figure can be viewed in color online via www.interscience.wiley.com.]

need for an occluding balloon. Such a saline flush would be necessary in vivo as blood would severely degrade the image quality.

The intravascular image created in such a system would likely only visualize the media and adventitia layers in the larger scan angles of the image due to the limited imaging depth of OCT. Despite this limitation, the ability to resolve the different arterial layers as well identify constituents of the occlusion and identify microchannels would add a valuable tool to the interventionist's arsenal.

TABLE 1. OCT Signal Characteristics of CTO Constituents

CTO component	OCT appearance
Perivascular tissue (loose connective tissue surrounding the artery)	Dark border surrounding the artery
Adventitia	Signal rich peripheral border of the vessel
Media	Signal rich in significant fibrosis or signal poor when it maintains its muscular nature
Collagen within the lumen	Uniformly back-scattering region. Denser collagen has a higher back-scattering signal (Figs. 3 and 4)
Smooth muscle cells within the lumen	Dark regions within the collagen matrix of the CTO. Not very reflective (Fig. 2)
Intraluminal microchannels	Fine cracks within the CTO. Residual blood shows as a bright reflective lining
Lipid	Lightly scattering in large pools; Can be identified also as small "segments" (Fig. 6)
Microcalcifications within the CTO	Highly reflective dots. When abundant, they create shadows (Fig. 5)
Intramural calcium	Highly reflective on the surface; otherwise signal poor (Fig. 4)

ACKNOWLEDGMENTS

REFERENCES

1. Stone GW, Kandzari DE, Mehran R, Colombo A, Schwartz RS, Bailey S, Moussa I, Teirstein PS, Dangas G, Baim DS, Selmon M, Strauss BH, Tamai H, Suzuki T, Mitsudo K, Katoh O, Cox DA, Hoye A, Mintz GS, Grube E, Cannon LA, Reifart NJ, Reisman M, Abizaid A, Moses JW, Leon MB, Serruys PW. Percutaneous recanalization of chronically occluded coronary arteries: A consensus document: Part I. Circulation 2005;112:2364–2372.

2. Kahn JK. Angiographic suitability for catheter revascularization of total coronary occlusions in patients from a community hospital setting. Am Heart J 1993;126:561–564.

3. King SB III, Lembo NJ, Weintraub WS, Kosinski AS, Barnhart HX, Kutner MH, Alazraki NP, Guyton RA, Zhao XQ. A randomized trial comparing coronary angioplasty with coronary bypass surgery. N Engl J Med 1994;331:1044–1050.

4. Safian RD, McCabe CH, Sipperly ME, McKay RG, Baim DS. Initial success and long-term follow-up of percutaneous transluminal coronary angioplasty in chronic total occlusions versus conventional stenoses. Am J Cardiol 1988;61:23G–28G.

5. Srivatsa SS, Edwards WD, Boos CM, Grill DE, Sangiorgi GM, Garratt KN, Schwartz RS, Holmes DR Jr. Histologic correlates of angiographic chronic total coronary artery occlusions: Influence of occlusion duration on neovascular channel patterns and intimal plaque composition. J Am Coll Cardiol 1997;29:955–963.

6. Katsuragawa M, Fujiwara H, Miyamae M, Sasayama S. Histologic studies in percutaneous transluminal coronary angioplasty for chronic total occlusion: Comparison of tapering and abrupt types of occlusion and short and long occluded segments. J Am Coll Cardiol 1993;21:604–611.

7. Strauss BH, Segev A, Wright GA, Qiang B, Munce N, Anderson KJ, Leung G, Dick AJ, Virmani R, Butany J. Microvessels in chronic total occlusions: Pathways for successful guidewire crossing? J Interv Cardiol 2005;18:425–436.

8. Bouma BE, Tearney GJ. Handbook of Optical Coherence Tomography, 1st edition. New York, NY: Marcel Dekker, 2002:15.

9. Fujimoto JG, Boppart SA, Tearney GJ, Bouma BE, Pitris C, Brezinski ME. High resolution in vivo intra-arterial imaging with optical coherence tomography. Heart 1999;32:128–133.

10. Patwari P, Weissman NJ, Boppart SA, Jesser C, Stamper D, Fujimoto JG, Brezinski ME. Assessment of coronary plaque with optical coherence tomography and high-frequency ultrasound. Am J Cardiol 2000;85:641–644.

11. Jang IK, Tearney GJ, MacNeill B, Takano M, Moselewski F, Iftima N, Shishkov M, Houser S, Aretz HT, Halpern EF, Bouma BE. In vivo characterization of coronary atherosclerotic plaque by use of optical coherence tomography. Circulation 2005;111:1551–1555.

12. Hoye A, Onderwater E, Cummins P, Sianos G, Serruys PW. Improved recanalization of chronic total coronaryocclusions using an optical coherence reflectometry-guided guidewire. Catheter Cardiovasc Interv 2004;63:158–163.

13. Ng W, Chen WH, Lee PY, Lau CP. Initial experience and safety in the treatment of chronic total coronary occlusions with a new optical coherent reflectometry-guided radio-frequency ablation guidewire. Am J Cardiol 2003;92:732–734.

14. Baim DS, Braden G, Heuser R, Popma JJ, Cutlip DE, Massaro JM, Marulkar S, Arvay LJ, Kuntz RE. Utility of the safe-cross-guided radiofrequency total occlusion crossing system in chronic coronary total occlusions (Results from the Guided Radio Frequency Energy Ablation of Total Occlusions Registry Study). Am J Cardiol 2004;94:853–858.

15. Wong P, Tse KK, Chan W. Recanalization of chronic total occlusion after conventional guidewire failure: Guided by optical coherent reflectometry and facilitated by radiofrequency energy ablation. J Invas Cardiol 2004;16:54–57.

16. Yang VX, Gordon ML, Qi B, Pekar J, Lo S, Seng-Yue E, Mok A, Wilson BC, Vitkin IA. High speed, wide velocity dynamic range Doppler optical coherence tomography (Part I): System design, signal processing, and performance. Opt Express 2003;11:794–809.

17. Yun YH, Tearney GJ, de Boer JF, Iftimia N, Bouma B. High-speed optical frequency-domain imaging. Opt Express 2003;11:2953–2963.

18. Cilingiroglu M, Oh JH, Sugunan B, Kemp NJ, Kim J, Lee S, Zaatari HN, Escobedo D, Thomsen S, Milner TE, Feldman MD. Detection of vulnerable plaque in a murine model of atherosclerosis with optical coherence tomography. Catheter Cardiovasc Interv 2006;67:915–923.

19. Kume T, Akasaka T, Kawamoto T, Ogasawara Y, Watanabe N, Toyota E, Neishi Y, Sukmawan R, Sadahira Y, Yoshida K. Assessment of coronary arterial thrombus by optical coherence tomography. Am J Cardiol 2006;97:1713–1717.

20. Noguchi T, Miyazaki MDS, Morii I, Daikoku S, Goto Y, Nonogi H. Percutaneous Transluminal Coronary Angioplasty of Chronic Total Occlusions. Determinants of primary success and long-term clinical outcome catheter. Cardiovasc Interv 2000;49:258–264.

21. Dong S, Smorgick Y, Nahir M, Lotan C, Mosseri M, Nassar H, Gotsman MS, Hasin Y. Predictors for successful angioplasty of chronic totally occluded coronary arteries. J Interv Cardiol 2005;18:1–7.

22. Strauss BH, Goldman L, Qiang B, Nili N, Segev A, Butany J, Sparkes JD, Jackson ZS, Eskandarian MR, Virmani R. Collagenase plaque digestion for facilitating guide wire crossing in chronic total occlusions. Circulation 2003;108:1259–1262.

23. Boppart SA, Bouma BE, Pitris C, Tearney GJ, Fujimoto JG, Brezinski ME. Forward-imaging instruments for optical coherence tomography. Opt Lett 1997;22:1618–1620.

24. Liu X, Cobb MJ, Chen Y, Kimmey MB, Li XD. Rapid-scanning forward-imaging miniature endoscope for real-time optical coherence tomography. Opt Lett 2004;29:1763–1765.

25. Wang T, Bachman M, Li GP, Guo S, Wong BJ, Chen Z. Low-voltage polymer-based scanning cantilever for *in vivo* optical coherence tomography. Opt Lett 2005;30:53–55.

26. Wu J, Conry M, Gu C, Wang F, Yaqoob Z, Yang C. Paired-angle-rotation scanning optical coherence tomography forward-imaging probe. Opt Lett 2006;31:1265–1267.

27. Huber R, Wojtkowski M, Fujimoto JG. Fourier Domain Mode Locking (FDML): A new laser operating regime and applications for optical coherence tomography. Opt Lett 2006;14:3225–3237.