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Review Article

Optical Coherence Tomography in Coronary Artery Disease: Toward Sub cellular Imaging

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Abstract

Intracoronary optical coherence tomography (OCT) is an interferometric imaging technology that uses near-infrared light to provide cross-sectional images with an axial resolution of 10 μm and a transverse of 20-40 μm in vivo. The imaging capabilities of OCT have enabled visualization of important features of coronary plaque, including thrombus, macrophage, neovascularization, stent implantation and stent strut coverage, which have provided new insights for better understanding of this disease. Frequency domain (FD)-OCT is second-generation form of OCT that is able to acquire OCT images at a much higher frame. The high-speed imaging capabilities of FD-OCT have made intravascular OCT practical and the introduction of this new technology is expected to help cardiologists make more informed decisions on coronary interventions. Recently, a new form of OCT, termed micro-optical coherence tomography (μOCT), has been developed, which affords a ten-times spatial resolution improvement compared conventional OCT systems. μOCT has shown to be capable of imaging sub cellular features of coronary artery that are relevant to atherosclerosis, including leukocyte adhesion and diapedesis, fibrin and platelet accumulation, and individual macrophages, smooth muscle cells, and cholesterol crystals. In addition, μOCT is capable of evaluating stent struts and the body's reaction to implantable devices in much greater detail than previously possible. These unique capabilities of μOCT could make it a useful tool for understanding and diagnosing coronary artery disease at the cellular level.

Keywords: Optical Coherence Tomography; Atherosclerosis; Coronary Artery

Introduction

Optical coherence tomography (OCT) is an emerging optical imaging modality that performs high-resolution cross-sectional imaging of tissue microstructure *in situ* in real-time [1]. When applied to cardiology, OCT can visualize coronary pathology with a transverse resolution of 20-40 μm and an axial resolution of ~10 μm, which are one to two orders of magnitude better than intravascular ultrasound (IVUS). Similar to IVUS, OCT measures time-of-flight of back-reflected radiation from the coronary wall to construct a depth-resolved reflectivity profile. OCT images are higher in resolution than IVUS because the propagation of light is faster than sound. Scanning the beam along the arterial wall generates a three-dimensional volumetric data set that captures comprehensive micro structural information of the coronary artery.

There are two implementations of OCT referred to as time-domain (TD)-OCT and frequency-domain (FD)-OCT [2-5]. In TD-OCT system, light from a broadband light source (around 1300 nm wavelength) is split into a sample arm that is focused on the coronary wall and a reference arm that is sent to a moving reference mirror. The back-reflected light from the sample and reference arms are recombined at a single detector. When the optical path difference between light reflected from various structures in the coronary wall (sample arm) and the reference arm are within coherence parameter of the light source termed its coherence length, the light from these two arms combine and form an interference pattern. Depth-resolved arterial structure is constructed by recording the interferometric intensity as a function of reference mirror distance as it is moved. An OCT image is generated by successively moving the focus to a new location on the coronary wall and performing a TD-OCT scan.

Many of the seminal studies that established OCT as an intracoronary diagnostic imaging technology were conducted with TD-OCT. Using cadaver specimens, TD-OCT *ex vivo* studies demonstrated OCT's ability to visualize the three-layered structure of a coronary artery and established criteria for diagnosing coronary atherosclerosis [6]. Post mortem studies revealed that OCT could distinguish different types of coronary artery plaques with high sensitivity and specificity [7]. Furthermore, a number of important hallmarks of the disease such as macrophage accumulations, thrombus classification, cholesterol crystals, calcium deposition, fibrous caps, and lipid cores could be visualized [8-11].

Because of OCT's superior contrast and resolution, this technology is able to assess coronary stents following placement. In a swine study conducted in 2000, OCT was able to more accurately detect artery dissection, tissue prolapsed and malapposition than IVUS [12]. The first-in-human OCT imaging case was reported in 2002 [6] with a number of clinical pilot studies [13-16]. From these *in vivo* OCT studies, we have gained a more detailed understanding of human atherosclerotic plaques, thrombus formation, macrophage distributions, neovascularization, stent implantation and stent strut coverage in coronary artery disease [13-21]. In particular, OCT clinical

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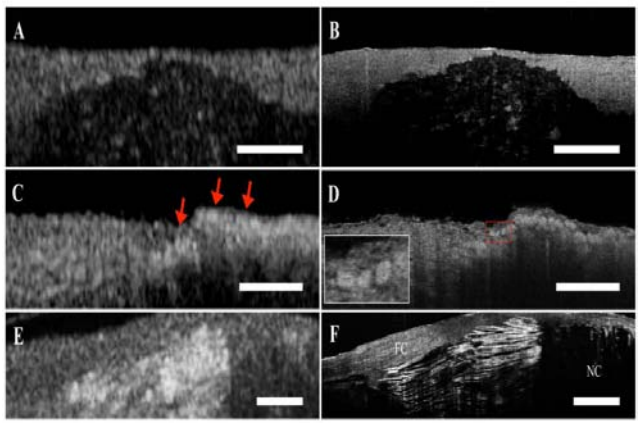

Figure 1: Corresponding μOCT and FD-OCT images of human coronary artery *ex vivo*.
(A,B) Comparison between corresponding FD-OCT and μOCT images of a calcium plate within coronary artery wall. (C) Foam cells imaged by FD-OCT appear as highly scattering, ill-defined punctate regions (red arrows). (D) Corresponding μOCT image of foam cells. μOCT clearly visualizes each foam cell individually, which appear as highly scattering round or ellipsoidal structures (Left lower inset) that contain smaller low signal regions within, consistent with nuclei. (E) Necrotic fibroatheroma with cholesterol crystal by FD-OCT. (F) Cholesterol crystals are characterized by intense reflections from their top and bottom surfaces on μOCT. Scale bar, 200 μm. FC; Fibrous Cap, NC; Necrotic Core.

trials have contributed to understanding the morphological features associated with acute coronary syndrome (ACS), caused by plaque rupture and thrombus formation. OCT is a unique intracoronary imaging technology that has demonstrated the ability to quantify the thickness of a thin fibrous cap and to detect the presence of a large lipid pool and macrophage infiltration within fibrous cap, all of the pathological hallmarks of high-risk or vulnerable plaques that are thought to be precursors of ACS and AMI [22]. In addition, *in-vivo* OCT studies have shown the capability of this technology to study key factors presumably related to the prognosis of stent-implanted lesions, including stent strut coverage, neointimal hyperplasia, stent mal apposition [23,24] and in-stent neoatherosclerosis [25,26].

Widespread clinical adoption of TD-OCT was limited due to slow acquisition speed, typically 4-8 frames per second. As a result, most TD-OCT imaging studies required balloon occlusion of the coronary with flushing to remove blood from the field of view. This balloon occlusion technique limited the applicability of IVOCT because of long scan times with a potential for inducing coronary damage or myocardial ischemia.

A major technical breakthrough in IVOCT occurred with the development of Fourier-Domain (FD)-OCT, a second-generation form of OCT that is able to obtain OCT images with a much higher frame rate compared with TD-OCT, while maintaining excellent image quality. There are two types of FD-OCT; one that utilizes a wavelength swept laser source, often referred to as SS-OCT or optical frequency domain imaging (OFDI), and another that utilizes a broad bandwidth optical source termed spectral-domain systems (SD-OCT). In SS-OCT or OFDI systems, the reference mirror is fixed so that the reference and sample arm path lengths are roughly equivalent. The light source has a narrow instantaneous line width but its wavelength is rapidly swept over a broadband spectral range. Each wavelength component is undergoes interference between the back-reflected light of the sample and reference arm. Applying a Fourier transform to the spectral interference pattern yields an OCT reflectively profile and the depth-resolved coronary structure. Because the swept source laser can be tuned more rapidly than the reference mirror can be moved in TD-OCT, the OFDI frame rate is greater than that of TD-OCT by 1-2 orders of magnitude, which enables the acquisition of three-dimensional comprehensive volumetric microscopy of long arterial segment following a safely administered single 8-10 cc saline or radio contrast flush.

The initial demonstration of intracoronary OFDI *in-vivo* was performed in a swine in 2006 [5]. After FDA approval of the OFDI catheter, the first clinical study was conducted in 2008 [27]. Following this initial demonstration, IVOCT products based on this technology have been commercialized and are widely available for use in interventional cardiology. The near term goal for this technology is to improve outcomes for coronary intervention and follow the response of stent deployment [28,29]. To date, adoption of OFDI by leading cardiovascular centers is growing due to the improvements in the technology and efforts to standardize technology among different cardiovascular research centers and manufacturers [30].

Although OCT provides greater than an order of magnitude increase in resolution over IVUS, higher-resolution images are required to further explore cellular-level responses to coronary atherosclerosis. We have recently demonstrated a new higher-resolution form of OCT, termed micro-optical coherence tomography (μOCT), which affords ten-time better spatial resolution than that of conventional FD-OCT systems [31]. Based on a form of spectral-domain (SD)-OCT, μOCT differs from OFDI in that it uses a larger spectral bandwidth and shaped optical beam that illuminates the artery wall, which produces high resolution images in both axial (≤1

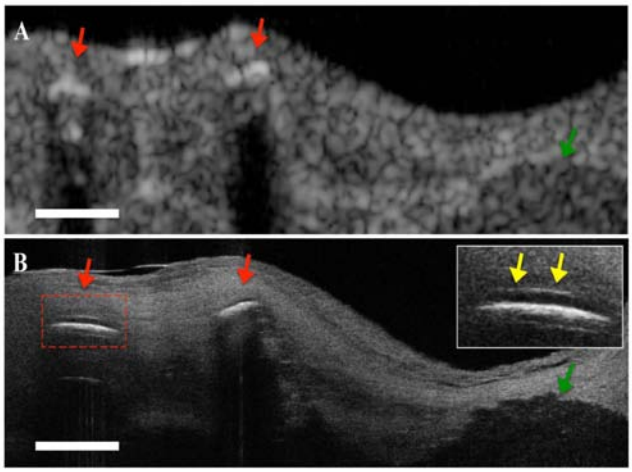

Figure 2: Comparison μOCT and FD-OCT images of stent implanted coronary lesion *ex vivo*.
(A) OFDI image. Stent struts (red arrows) and calcified lesion (green arrow) can be seen. (B) Corresponding μOCT image. Drug eluting stents showing polymer (yellow arrows) overlying the strut reflections (top right inset) and calcified lesions were observed. Scale bar, 200 μm.

μm) and lateral (≤2 μm) directions. With this improved resolution, μOCT has demonstrated the ability to visualize subcellular features of coronary artery relevant to atherosclerosis *ex vivo*, including leukocyte adhesion and diapedesis, fibrin and platelet accumulation, macrophage, smooth muscle cells, and cholesterol crystals (Figure 1). In addition, μOCT has been shown *ex vivo* to be capable of evaluating polymer coating overlying stent struts (Figure 2) as well as inflammatory cell infiltrations around these devices. Current μOCT research is focused on the development of a catheter that is capable of acquiring this information *in* vivo. Once intravascular μOCT is available, it is likely that the cellular and subcellular resolution of this technology will provide significant insight into the nature of human coronary artery disease, will provide superior diagnostic capabilities for the prospective prevention of ACS and AMI, and will enable the design and understanding of the arterial response to implanted coronary medical devices.

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