Review

Assessment of Coronary Atherosclerosis using Optical Coherence Tomography

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Optical coherence tomography (OCT) is a catheter-based imaging system that uses near-infra-red light to produce cross-sectional images of the coronary arteries. With its extraordinarily high resolution (10-20 μm), OCT allows clinicians to observe various morphological features of coronary atherosclerosis in vivo. For example, intimal thickening presents as homogeneous, signal-rich regions on OCT, while fibroatheroma with a lipid-rich necrotic core is characterized by the presence of signal-poor regions with a diffuse border. Furthermore, plaque rupture is detected in 50〜70% of culprit lesions of acute coronary syndrome (ACS), and plaque erosion develops over areas of intimal thickening and/or thick-cap fibroatheroma. Meanwhile, calcified nodules are common in older patients with hypertension and chronic renal disease. Platelet-rich thrombi are visualized as low backscattering structures and often detected in patients with unstable angina, whereas red blood cell-rich thrombi exhibit a high backscattering structure with signal-free shadowing and are frequently noted in patients with acute myocardial infarction. Moreover, OCT-derived thin cap fibroatheroma has been shown to be a predictor of subsequent plaque progression and acute coronary events, while vasa vasorum and the macrophage density are associated with a thin fibrous cap and large necrotic core as well as increased serum levels of inflammatory biomarkers. One current challenge of OCT examinations is to detect morphologic characteristics capable of discriminating vulnerable from stable plaques. The ability to detect vulnerable plaques in vivo would allow physicians to identify patients at high risk for adverse coronary events, thus significantly helping to prevent ACS.


Key words: Optical coherence tomography, Coronary, Atherosclerosis, Vulnerable plaque

Introduction

The detection and treatment of coronary artery atherosclerosis represents a main focal point for clinical cardiologists and cardiovascular researchers. The accumulation of atheromatous plaque progressively narrows the coronary artery lumen and impairs the myocardial blood flow, and consequent plaque rupture and intracoronary thrombosis result in acute coronary syndrome (ACS). Over the past decade, the findings of histological studies of patients with ACS have evolved our understanding of the pathophysiology of coronary artery disease. However, the major limitation of histological studies is the lack of direct, longitudinal assessments in a prospective model. Recently, several intravascular imaging modalities have been developed to assess the degree of coronary atherosclerosis in vivo. As catheter examinations can be performed repeatedly at sequential time points, intravascular imaging is suitable for assessing serial changes in coronary plaques. Optical coherence tomography (OCT) is a novel technique that enables clinicians to determine the plaque composition and has the potential to detect “vulnerable” thrombosis-prone plaques.

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Table 1. Criteria for plaque characterization on OCT

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<td>Signal-rich layer near lumen</td>
</tr>
<tr>
<td>Media</td>
<td>Signal-poor layer in middle of artery wall</td>
</tr>
<tr>
<td>Adventitia</td>
<td>Signal-rich outer layer of artery wall</td>
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<tr>
<td>Fibrous</td>
<td>Signal-rich, homogeneous region</td>
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<tr>
<td>Calcification</td>
<td>Signal-poor, well-delineated region</td>
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<tr>
<td>Lipid</td>
<td>Signal-poor, poorly delineated region</td>
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<tr>
<td>Fibrous-cap</td>
<td>Signal-rich layer overlying signal-poor region</td>
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<td>Plaque rupture</td>
<td>Fibrous-cap discontinuity and a cavity formation</td>
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<td>Erosion</td>
<td>Irregular luminal surface with thrombi</td>
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<td>Lipidic plaque with fibrous cap of &lt;65 μm thick</td>
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<td>Low-backscattering protrusion</td>
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<td>Vasa vasorum</td>
<td>Signal-poor, well-delineated void within plaque</td>
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<td>Macrophages</td>
<td>Signal-rich, distinct or confluent punctate regions with shadowing</td>
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This review summarizes the characteristics of OCT assessments of coronary atherosclerosis.

**Optical Coherence Tomography**

OCT is a catheter-based imaging system that uses near-infrared light to produce cross-sectional images of the coronary arteries. As near-infrared light is unable to penetrate red blood cells (RBCs), OCT imaging is performed in a blood-free environment with the bolus injection of contrast medium. The high frame rate of OCT enables the clinicians to image long coronary segments for a few seconds. At present, two OCT systems, Frequency-domain OCT (St. Jude Medical, St. Paul, Minnesota, USA) and Frequency Domain Optical Imaging (Terumo, Tokyo, Japan), are clinically available. The greatest advantage of OCT is its resolution of 10-20 μm, which is approximately 10 times higher than that of intravascular ultrasound (IVUS). With its extraordinarily high resolution, OCT allows physicians to observe various morphological features of coronary atherosclerosis in vivo (Table 1).

**Imaging of Coronary Atherosclerosis**

**Intimal Thickening**

The coronary artery wall consists of three layers: the intima, media and adventitia. While IVUS cannot be used to identify the boundary between the intima and media, OCT shows the intima as the signal-rich layer nearest the lumen, the media as the signal-poor middle layer and the adventitia as the signal-rich outer layer of the artery wall. Intimal thickening with the accumulation of smooth muscle cells occurs in the early phase of atherosclerosis, subsequently progressing to preatheroma with fatty streaks and pools of extracellular lipids.

**Fibroatheroma**

Fibroatheroma is characterized by the presence of a lipid-rich necrotic core with an overlying fibrous cap. OCT can be used to identify the major tissue components of fibroatheromas, including fibrous tissue, lipid and calcium. On OCT, fibrous tissue is visualized as homogeneous, signal-rich regions, while lipids present as signal-poor regions with a diffuse border and calcium exhibits signal-poor regions with a sharp border. OCT enables the clinician to obtain accurate measurements of the fibrous cap thickness, which shows an excellent correlation with the findings of histological examinations. In addition, the necrotic core size may be semi-quantified by measuring the lipid arc on cross-sectional images, as the attenuation of OCT signals behind lipids prevents the visualization of the entire necrotic core. The OCT-measured fibrous cap thickness and necrotic core size are important determinants of plaque vulnerability.

**Plaque Rupture**

OCT is a feasible and safe imaging modality in patients with ACS and provides the opportunity to detect plaque rupture in vivo (Fig. 1). Plaque rupture is characterized by the presence of fibrous cap discontinuity and cavity formation within the plaque, being detected on OCT in 50–70% of culprit lesions of
Erosion

OCT has the unique ability to visualize plaque erosion, which is characterized by the presence of an irregular luminal surface with thrombi (Fig. 2). Plaque erosion is detected on OCT in 20~30% of culprit lesions of ACS. The majority of sites of erosion occur over areas of intimal thickening and/or thick intima of ACS. The thickness of the ruptured fibrous cap measured on OCT is ~140 μm, which is thicker than that reported in histological studies. Plaque rupture is often observed in non-culprit lesions of ACS, representing the effects of a pan-coronary process of vulnerable plaque development. In addition, plaque rupture may be noted in patients with stable coronary artery disease. OCT may be used to assess two features linking plaque rupture to ACS: a large necrotic core and a small lumen.

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signal-free shadowing. In addition, platelet-rich thrombi are often observed in patients with unstable angina, while RBC-rich thrombi are frequently detected in those with acute myocardial infarction.

**Thin Cap Fibroatheroma**

The hypothesized precursor lesions associated with plaque rupture are termed “thin cap fibroatheromas” (TCFAs) or “vulnerable plaques.” TCFA is characterized by the presence of a large necrotic core with a thin fibrous cap measuring <65 μm with associated inflammatory cell infiltration and positive remodeling. The high resolution of OCT enables the clinician to identify the thin fibrous cap of TCFA in vivo (Fig. 4 and 5), and OCT-derived TCFA lesions are associated with various features of plaque vulnerability on conventional imaging techniques, such as the accumulation of attenuated plaque on gray-scale IVUS, necrotic core-rich plaque on virtual histology IVUS, yellow color plaque on angioscopy and low-density plaque on coronary computed tomography.

In addition, platelet-rich thrombi are often observed in patients with unstable angina, while RBC-rich thrombi are frequently detected in those with acute myocardial infarction.

**Calcified Nodules**

Recently, an OCT study reported the diagnosis of calcified nodules in the clinical setting. OCT-derived calcified nodules are defined as being indicative of fibrous cap disruption over sites of calcified plaque characterized by protruding areas of calcification as well as superficial calcium deposition with substantial calcium accumulation proximal and/or distal to the lesion (Fig. 3). The incidence of calcified nodules has been reported to be 7.9% in patients with ACS, with these distinctive lesions being more frequently observed in older patients (>65 years of age) with hypertension and chronic renal disease.

**Thrombi**

Intracoronary thrombosis is the major cause of ACS. At sites of plaque rupture, erosion or calcified nodule formation, platelets attach to the vessel wall, leading to fibrin polymerization (platelet-rich thrombosis). Fibrin networks trap RBCs, thus forming occlusive thrombi (RBC-rich thrombi). OCT can be used to determine the presence, location and size of a thrombus and even discriminate between platelet- and RBC-rich thrombi. Platelet-rich thrombi present with a low backscattering structure, whereas RBC-rich thrombi exhibit a high backscattering structure with

**Vasa Vasorum**

In atherosclerotic coronary arteries, the vasa vasorum proliferates from the adventitia into the arterial
Fig. 4. Relationship between TCFA and plaque rupture
Serial OCT examinations conducted at baseline and three weeks of follow-up show fibrous cap disruption in a TCFA lesion (A) progressing to plaque rupture (B) in the proximal RCA (arrows). The asterisks indicate lipid tissue, the arrowheads indicate the normal arterial wall.

Fig. 5. Relationship between TCFA and plaque rupture
Serial OCT examinations conducted at baseline and two weeks and seven months of follow-up show fibrous cap disruption in a TCFA lesion (A) progressing to plaque rupture with thrombosis (arrowhead) (B) and plaque ulceration (C) in the mid RCA (arrows). The asterisks indicate lipid tissue.
blood cell count and presence of TCFA. Therefore, OCT provides valuable information for assessing plaque vulnerability based on its ability to identify macrophages.

**Spontaneous Coronary Artery Dissection (SCAD)**

The potential for SCAD should be suspected in young women without classical coronary risk factors presenting with ACS. Although diagnosing SCAD remains a major challenge, OCT can be used to detect SCAD, especially in cases in which the features of the condition are not angiographically apparent (Fig. 7). OCT enables the precise visualization of intimal tears as well as the differentiation of true from false lumens and the determination of the location of intramural dissection. Recent reports recommend the use of OCT to diagnose and treat patients with SCAD. Although OCT requires flushing of the lumen, as in angiography, the current FD-OCT system allows physicians to explore the entire length of the coronary artery using a small amount of flush medium. Considering the insufficient diagnostic capability of angiography for detecting SCAD, it may be better to apply FD-OCT rather than administer several injections of wall in order to supply nutrition to the lesion. Furthermore, the vasa vasorum functions as a pipeline for cholesterol and macrophages into plaques. On OCT, the vasa vasorum is visualized as a no-signal micro-channel within the plaque (Fig. 6), and the OCT-derived vasa vasorum is associated with a thin fibrous cap, large necrotic core and increased serum level of high-sensitivity C-reactive protein. Because the vasa vasorum contributes to the development of intraplaque hemorrhage, plaque rupture and mural thrombosis, its detection is a useful marker for identifying vulnerable plaques.

**Macrophages**

Local increases in the macrophage content in the thin fibrous cap promote atherosclerotic plaque instability. OCT visualizes macrophages as signal-rich bands with signal-free shadowing (Fig. 6). Patients with ACS have significantly higher macrophage densities in the culprit lesions compared to individuals with stable coronary artery disease, and sites of plaque rupture display greater macrophage densities than those without. Furthermore, the macrophage density in the fibrous cap is associated with the white blood cell count and presence of TCFA. Therefore, OCT provides valuable information for assessing plaque vulnerability based on its ability to identify macrophages.

**Fig. 6.** Macrophages and the vasa vasorum

OCT performed at baseline shows a lesion with macrophage infiltration (arrows) and the vasa vasorum (arrowhead) in the mid LAD. Eight months later, the patient presented with ACS, and angiography demonstrated coronary occlusion in the mid LAD (asterisk). SB = septal branch.
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OCT-derived erosion, calcified nodules and the vasa vasorum were established according to pathological findings, taking into account the limitations of OCT.

Future Developments in OCT Technology

OCT provides images with less motion artifacts than IVUS, due to its faster frame rate and pullback speed, both of which enable the three-dimensional visualization of the coronary arteries. Three-dimensional visualization is a powerful tool for representing OCT data that helps to develop our understanding of vessel and plaque morphology. In addition, next-generation OCT devices in which the resolution is improved by 1 μm have been developed. The ultra-high resolution of next-generation OCT is expected to offer clear pictures of the cellular and subcellular features associated with atherogenesis. Furthermore, automated methods for plaque characterization are currently under development. The application of a post-processing color-coding software-based algorithm based on the analysis of either spectral OCT backscattered data or other optical tissue properties is also anticipated to improve the ability to both identify and characterize the sites of atherosclerotic coronary plaque.

X-ray contrast for angiography when attempting to make an accurate diagnosis.

Limitations of OCT

Positive arterial remodeling is a predominant feature of culprit lesions of ACS. Lesions positive for remodeling exhibit the histological characteristics of vulnerable plaques, including a large necrotic core and high macrophage content. Because the depth of penetration of near-infrared light is limited to <2 mm, OCT cannot be used to visualize the whole-vessel structure of lesions with a large plaque burden. Compared to OCT, IVUS displays a greater penetration depth and is therefore more suited to assessing coronary arterial remodeling. A recent clinical study of OCT and IVUS demonstrated that 67% of OCT-derived TCFAs present with positive remodeling.

The definitions of plaque erosion, calcified nodules and the vasa vasorum, as detected on OCT, have not been validated by pathology. In addition, OCT cannot be used to identify a lack of endothelial cell lines or the proliferation of a tiny vasa vasorum (<10 μm), as these structures lie below the resolution of OCT scanners. Furthermore, the shallow depth of penetration of OCT precludes the ability to visualize deep fractured calcified plates. Therefore, the diagnostic criteria for detecting sites of OCT-derived erosion, calcified nodules and the vasa vasorum were established according to pathological findings, taking into account the limitations of OCT.

Fig. 7. Spontaneous coronary artery dissection (SCAD)

Angiography shows diffuse lumen narrowing in the mid to distal RCA. OCT demonstrates coronary dissection, including intimal tearing (arrowheads) (A, D) and a small true lumen (asterisks) compressed by a large intramural false lumen (daggars) (B, C).
Conclusions

The development of OCT has evolved our understanding of the pathophysiology of coronary atherosclerosis. A current challenge of OCT examinations is to detect morphologic characteristics capable of discriminating vulnerable from stable plaques. The detection of vulnerable plaques in vivo allows for the identification of patients at high risk for adverse coronary events, which may have a significant impact on the ability to prevent ACS.

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COI

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