Assessment of Coronary Plaque Vulnerability with Optical Coherence Tomography

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Several catheter-based imaging modalities have been developed over the past 2 decades for visualizing the morphological features of coronary atherosclerotic plaques that are susceptible to future development of serious cardiovascular events. Optical coherence tomography (OCT) is a new high-resolution intracoronary imaging modality based on near-infrared interferometry, and it has been shown to be able to identify various components of atheromatous plaques. In this review, we examine the histopathology of vulnerable plaques as a target for imaging technology, and discuss the evidence of OCT in identifying vulnerable atherosclerotic lesions in patients with coronary artery disease.

Key Words: Coronary artery disease • Optical coherence tomography • Vulnerable plaque

It is well recognized that the culprit lesions in patients with acute coronary syndrome (ACS) are usually characterized by advanced atherosclerotic changes with concomitant thrombus formation. The term “vulnerable plaque” is used to specify a high-risk plaque susceptible to the development of either rapid luminal stenosis or occlusive intraluminal thrombus, those lead to catastrophic cardiovascular events. Over the past 2 decades, considerable effort has been made to identify such high-risk coronary plaques before their rupture for the prevention of the critical coronary events. In recent years, catheter-based intravascular imaging technologies, especially intravascular optical coherence tomography (OCT), have shown particular progress. Compared with non-invasive or other invasive technologies, intravascular OCT has advantages in terms of higher spatial resolution, precise plaque localization, and real-time image processing. This review focuses on the usefulness of OCT for the evaluation of plaque vulnerability in patients with coronary artery disease.

OCT TECHNOLOGY

OCT is a relatively new high-resolution intracoronary imaging technology based on near-infrared interferometry. The spatial resolution of OCT, nearly 10 μm on the lateral axis, is almost 10 times greater than that of intravascular ultrasound (IVUS). At present, 2 types of OCT systems, time domain (TD)- and Fourier domain (FD)-OCT, are available for clinical use. TD-OCT is a conventional type of intravascular device, and this system incorporates near infrared light source and optical components that operate in a wavelength on 1,310 nm. Rather than using a broadband light source as in conventional TD-OCT systems, FD-OCT imaging systems employ a wavelength-swept laser as a light source, and this improvement enables faster image acquisition speeds and greater scan depths (Table 1). In addition, the higher pull-back speed of FD-OCT can prevent heart motion artifacts and thus allow precise assessment of the longitudinal distribution of plaque components.
As shown in Figure 1, OCT visualizes 3 layer structures of normal coronary artery as well as plaque component of atherosclerotic lesions. The ability of OCT in tissue characterization of coronary atherosclerotic lesions has been well validated in clinicopathological studies. In addition, the drawback points of OCT are the relatively shallow depth of light penetration into the arterial wall in the comparison with ultrasound, and the necessity of blood removal by contrast medium during image acquisition.

PATHOLOGICAL BACKGROUND OF PLAQUE VULNERABILITY

Medical term “vulnerable plaque” was first used by Muller et al. in defining the plaque with rupture that is one of the triggers for the onset of acute cardiovascular disease. In fact, pathological studies of the victims of sudden cardiac death have revealed that more than 70% of ACS are attributable to the formation of occlusive thrombus that is preceded by plaque rupture. However, as noted in these autopsy studies, plaque rupture is not the sole pathological cause of coronary events; no rupture was seen in the remaining 30% of the culprit lesions, which instead showed features such as plaque erosion or calcified nodules. In current clinical practice, these non-rupture-type features in baseline lesions are also considered to be characteristics of vulnerable coronary plaques (Table 2). In clinical setting, OCT is able to visualize plaque morphology possibly agree with autopsy findings (Figure 2). Furthermore, recent studies have shown that vulnerable plaques can develop not only in native coronary arteries but also in the neointima after long-term coronary stent implantation.

Table 1. Platform comparison between time domain (TD)- and Fourier domain (FD)-optical coherence tomography (OCT)

<table>
<thead>
<tr>
<th>Pullback Mode</th>
<th>TD-OCT</th>
<th>FD-OCT (ILUMIEN OPTIS)</th>
</tr>
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<tr>
<td>Engine speed</td>
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<td>180 fps</td>
</tr>
<tr>
<td>Pullback speed</td>
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<td>500</td>
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<td>Scan diameter</td>
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Table 2. Pathological features of vulnerable plaque

I. Macroscopic features
- Large necrotic or lipid core
- Luminal thrombus
- Plaque hemorrhage
- Spotty calcification
- Positive vascular remodeling

II. Microscopic features
- Thin fibrous cap covering lipid core
- Macrophage infiltration
- Plaque neovascularization
- Endothelial denudation
- Smooth muscle cell apoptosis
- Protease expression
- Endothelial adhesion molecule expression

III. Heat generation

Figure 1. OCT findings of normal coronary artery. Note. Clear differentiation of 3 layers in vessel wall.

Figure 2. Representative OCT findings plaque observed in patients with acute coronary syndrome. (A) Plaque rupture. Arrow indicates disrupted fibrous cap. * Represents space previously contained lipid pool. (B) Plaque erosion with thrombus formation (arrow). (C) Calcified nodule (arrow).
Plaque rupture

As previously described in the scientific literature, coronary arterial wall often develops significant atherosclerotic changes before the progression of luminal stenosis. Figure 3 shows the representative cross-sectional OCT images obtained from non-stenotic coronary plaque in patients with coronary artery disease (CAD). Among these complex characteristics, thin-cap fibroatheroma (TCFA) is known as a vulnerable plaque subtype which is susceptible to rupture. TCFA is pathologically diagnosed when the plaque has a large lipid or necrotic core (> 40% of total lesion cross-sectional area) and a thin fibrous cap (< 65 μm thick). An autopsy study of ruptured plaques in patients with sudden cardiac death found that 95% of these caps measured < 64 μm thick. Notably, a recent computer simulation study showed that fibrous cap thickness and necrotic core size are independent determinants for plaque disruption. Additionally, TCFA is frequently accompanied by macrophage infiltration and matrix metalloproteinase (MMP) expression in the fibrous cap covering the lipid core. Many studies have pointed out that high macrophage density is characteristic of lesions vulnerable to rupture. Ex vivo studies of human coronary artery plaques have shown that the density and pattern of macrophage infiltration at plaque shoulders correlate with degree of vulnerability. Chronic inflammation within TCFA also stimulates smooth muscle cell apoptosis within fibrous caps, development of calcification, and heat generation. Intraplaque new blood vessel formation is another unique morphological feature of TCFA, usually originating from the adventitial vasa vasorum. Intraplaque microvessels are immature and leaky due to the lack of basement membranes and pericytes, and their deterioration is known to cause intraplaque hemorrhage. This phenomena results in both rapid enlargement of plaque size and luminal stenosis. These histopathological features observed within TCFA are candidate targets for coronary artery imaging with the goal of detecting plaque vulnerability. However, it should also be noted that clinically silent plaque rupture is not rare.

Non-rupture type vulnerable plaque

Plaque erosion is characterized pathologically by a continuous intimal layer without rupture or discontinuation, usually accompanied by an intraluminal thrombus overlying a modestly occlusive plaque, although standard diagnostic criteria have not been defined. Typically, the endothelial cell layer is denuded and the exposed fibrous cap consists of smooth muscle cells, rich proteoglycans, and varying numbers of inflammatory cells. Autopsy data have demonstrated that plaque erosion is more frequent in women < 50 years of age, and lesions with such erosion are often negatively remodeled. Autopsy studies have shown that 20% to...
40% of acute coronary events are attributable to non-ruptured plaques, indicating that coronary thrombosis resulting from plaque erosions is not rare but is rather an unexpectedly common phenomenon. In current clinical practice it is difficult to diagnose plaque erosion using imaging technologies, because the pathogenesis of plaque erosion has not been elucidated and no currently available imaging modalities can differentiate the existence of endothelial cells covering atherosclerotic plaques. As yet there have been very few clinical studies targeting the role of plaque erosion in the development of ACS, except for a few case reports using OCT. Further research in both basic and clinical fields will be needed to precisely define plaque erosion and to determine its clinical significance.

Calcified nodules are a type of vulnerable plaque that account for approximately 2% to 7% of all coronary events. These nodules are defined pathologically as fibrocalcific plaques with disruption of the luminal surface, little or no underlying necrotic core, and thrombus formation overlying the calcified surface and protruding into the vascular lumen. The underlying plaques are usually characterized by heavy calcification and large plates of calcified matrix with surrounding areas of fibrosis, inflammation, and neovascularization. Interestingly, pathological examination has shown that these lesions are found predominantly in the mid-right coronary artery, where coronary torsion stress is maximal. Intravascular ultrasound (IVUS) and OCT examination are able to diagnose calcified nodules in coronary arteries. Although the calcified nodule has been categorized as a vulnerable plaque, a recent prospective clinical study using 3-vessel IVUS reported that this nodule type was not a predictor for major adverse events during 3 years of follow-up.

**Natural course of vulnerable plaques**

Until recently, morphological findings regarding vulnerable plaques had been limited in the context of autopsy studies. Coronary specimens are retrospectively analyzed after event occurrence, so it is difficult for pathological studies to investigate longitudinal changes in vulnerable plaques as well as the baseline plaque morphologies that cause future development of coronary events. Only modern imaging technologies in clinical practice are able to observe the natural history of coronary plaques with vulnerable characteristics.

A recent clinical study using serial virtual histology IVUS (VH-IVUS) reported that 75% of TCFA healed and 25% of TCFA maintained baseline characteristics during 12-month follow-up. It is important to note that not all vulnerable plaques progress to rupture, although the mechanism of TCFA healing is not well established.

Motoyama et al. performed computed tomography (CT) angiographic examinations on 1059 patients and prospectively followed them for 27 months for the development of ACS. Coronary lesions were analyzed for the presence of 2 features indicating plaque vulnerability: positive remodeling (lesion diameter at the plaque site ≥ 10% larger than that of the reference segment) and low attenuation plaques (noncalcified plaques with a density < 30 Hounsfield units). Although these features are not completely consistent with pathological studies, ACS developed in 22% of patients who had plaques with both vulnerability features at baseline, compared with 0.5% of patients who had plaques without these features. None of the patients with normal CT angiography developed ACS. The presence of 1- or 2-feature positive plaques was the only significant independent predictor of ACS.

**VULNERABLE PLAQUE IMAGING WITH OCT**

Conventional gray-scale IVUS has been used in catheterization laboratories for over 20 years. It is an established modality that is used not only for guidance during percutaneous coronary intervention (PCI), but also, in the context of clinical studies, for evaluating the tissue characteristics of coronary plaques and assessing plaque progression or regression. Its ability to provide precise qualitative and quantitative measurements of total plaque area and volume (burden), even in cases with positive vascular remodeling, make it invaluable for evaluating the vulnerability of coronary plaques. However, since conventional IVUS is limited to relatively low spatial resolutions (100-150 μm) and cannot accurately differentiate plaque components.

Because of its excellent spatial resolution, OCT is currently the only imaging technology that can precisely
measure the thickness of the fibrous cap and also directly visualize microvessels within coronary atherosclerotic plaques. Furthermore, OCT is able to identify macrophage infiltration in the plaque, an important feature of continuous inflammation in TCFA (Figure 3). The other advantage of OCT is its ability to detect intracoronary thrombi that are not usually well visualized by other imaging modalities. OCT not only visualizes thrombi, but can also distinguish between red and platelet-rich white thrombi.

**Vulnerable plaque in native coronary arteries**

In patients with CAD, TCFA was detected by OCT in 72% of cases with ST elevation myocardial infarction (STEMI) and 50% of those with non-STEMI culprit lesions, as compared to 20% of cases with stable angina pectoris lesions; the fibrous cap thicknesses in these 3 groups were reported to be 47, 54, and 103 μm, respectively. Furthermore, OCT examination after thrombus aspiration in patients with ACS revealed that 73% of patients showed plaque rupture, and the mean thickness of the ruptured fibrous cap was 49 μm. These OCT observations in patients with ACS correspond well with established pathological findings of vulnerable plaques that resulted in coronary events.

The incidence of secondary cardiovascular events is substantially higher in patients with previous ACS than in those with stable angina. Recent OCT study by Kato et al. showed that compared with non-culprit plaques in non-ACS patients, the number of lipid-rich plaques was greater in the ACS patients (1.9 in ACS patients vs. 1.1 in non-ACS patients, p = 0.022) In addition, it is reported that non-culprit plaques in ACS patients had a wider lipid arc, a longer lipid length, a thinner fibrous cap, and a higher prevalence of neovascularization. Moreover, TCFA (67.4% vs. 14.9%, p < 0.001), macrophage (88.2% vs. 37.9%, p < 0.001), and thrombus (23.5% vs. 0%, p < 0.001) were more frequent in ACS patients, suggesting that non-culprit plaques in ACS patients are more vulnerable than in non-ACS CAD patients.

Both diabetes mellitus (DM) and chronic kidney disease (CKD) are established risk factors for the development of ACS. Recent OCT study also has shown that compared with non-DM patients, DM patients have a larger lipid pool and a higher prevalence of calcification and thrombus. Especially, the lipid burden was larger and TCFA and macrophage were frequent in patients with inadequate glucose control of A1C > 8%. In CKD patients, it is reported that compared to non-CKD patients, the patients with CKD had a larger lipid burden with a higher prevalence of calcium, cholesterol-crystal and disruption.

**Neoatherosclerosis**

Recent studies have reported the development of neoatherosclerosis changes inside of both bare metal stents and drug eluting stents several years after implantation. These changes include lipid accumulation, calcium deposition, macrophage infiltration development of neovascularization within neointima area of the stent, and are assumed to play an important role in the development of late in-stent restenosis and late stent thrombosis that leads to secondary coronary events related to the culprit lesion (Figure 4). Although precise mechanisms in the development of neoatherosclerosis, Kato et al. recently showed that several factors independently predicted neoatherosclerosis, including stent age ≥ 48 months (odds ratio (OR) 2.65, 95% confidence interval (CI) 1.43-4.92), drug-eluting stents (DES, OR 2.65, 95% CI 2.41-13.24), age ≥ 65 years old (OR 1.91, 95% CI 1.05-3.44), current smoking (OR 2.30, 95% CI 1.10-4.82), chronic kidney disease (CKD: OR 4.17, 95% CI 1.42-12.23). In contrast, the use of angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists was a protective factor against neoatherosclerosis (OR 0.42, 95% CI 0.22-0.80). Although effective intervening treatment has not been established on neoatherosclerosis, these results may support the importance of secondary prevention after stent implantation.

Recent advance in OCT technology enable us to reconstruct 3 dimensional images of neointimal tissue and coronary stent. By using this technology, it is easy to recognize the spatial distribution of neointimal coverage of stent struts as well as neoatherosclerotic changes within the stent (Figure 5).

**Prediction of future development of ACS**

In the recent longitudinal, multicenter PROSPECT study, 693 ACS patients were evaluated using 3-vessel grayscale and VH-IVUS, and the relation between baseline IVUS characteristics of culprit and non-culprit
plaques and the secondary occurrence of major adverse cardiovascular events (MACE) at 3 years was studied. In this patient population, the MACE rate during 3 year follow-up was 20.4%, and these events were equally attributable to the progression of non-culprit lesions and to index culprit lesions treated by PCI. For MACE related to non-culprit lesions, no angiographic variables were associated with subsequent events. By contrast, the following IVUS and VH-IVUS baseline plaque parameters independently predicted the subsequent development of non-culprit lesion-related MACE: large plaque burden (≥ 70%), higher stenosis rate (minimal luminal area ≤ 4.0 mm²), or the presence of VH-IVUS detected TCFA. In addition, no events developed in coronary plaque segments with < 40% plaque cross-sectional area. However, even when all 3 predictive variables were present, the event rate rose to only 18.2%, indicating that although IVUS-derived characteristics suggest the occurrence of a subsequent event, they are not sufficient to predict which atheromas will undergo plaque progression. It is possible that the relatively low spatial resolution of IVUS failed to differentiate fine vulnerable structures in atheromatous non-culprit lesions, and that integration of systemic factors that influence plaque biology is necessary for more precise estimation of future ACS development.

However, specific OCT findings for predicting the future development of ACS have not been established. Uemura et al. examined the baseline OCT findings in non-stenotic coronary plaque within non-culprit coronary artery, and followed these plaques up to 12 months. In their study, baseline OCT findings of TCFA and micro-
channels were selected as independent predictors for subsequent angiographic progression of non-stenotic coronary plaques.57

**Limitations**

The major drawback of OCT is the relatively shallow penetration of light into the vascular wall, which necessitates the use of other modalities, such as IVUS and coronary CT, to evaluate total plaque volume and vessel remodeling. Although OCT seems to hold promise for evaluating the vulnerability of coronary atherosclerotic lesions, there have not yet been any prospective studies on the role of OCT-derived vulnerable plaques in the occurrence of future ACS. Large-scale clinical studies will be needed to show that high-risk plaques identified with this imaging techniques can significantly improve the outcome of patients compared with modern clinical practice using conventional biological predictors.

**CONCLUSIONS**

In this review article, we described the current and future role of OCT in the clinical management of coronary artery disease. Notably, since coronary plaque imaging by itself is not able to precisely predict the future occurrence of adverse outcome in patients with CAD, coordinating clinical data obtained by OCT with pathological and clinical laboratory findings will enhance our understanding of CAD and facilitate the future improvement in patient care. These efforts and further advances in imaging technology will hopefully enable us to precisely identify vulnerable plaques and to develop more effective treatments for vulnerable patients.

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**DISCLOSURES**

The authors have declared no potential conflicts of interest.

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