Evaluation of stent placement and outcomes with optical coherence tomography

Optical coherence tomography (OCT) is an imaging modality based on fiberoptic technology. OCT imaging systems use optical imaging catheters that emit near-infrared light to produce high resolution, real-time images. The frequencies and bandwidths of infrared light are far higher than medical ultrasound signals, resulting in greatly increased image resolution, which is approximately ten-times higher than that of intravascular ultrasound. Compared with conventional imaging modalities, OCT is superior for the evaluation of vulnerable plaque features, which may be associated with a higher risk of peri-interventional myocardial infarction, such as plaque rupture, thrombus, thin-capped fibroatheroma and macrophages within the fibrous caps. OCT can clearly visualize stent malapposition and tissue prolapse after stent deployment, as well as neointimal hyperplasia and persistent thrombus at follow-up. OCT provides new insight into the assessment and treatment of coronary artery disease with stent placement.

KEYWORDS: drug-eluting stent, frequency domain, guide for coronary intervention, optical coherence tomography, plaque characterization, time domain, vascular response

Coronary OCT usage in clinical settings

- Time-domain versus frequency-domain OCT

The only commercial time-domain OCT (TD-OCT) system available today consists of an OCT imaging probe (ImageWire™, LightLab Imaging Inc., MA, USA), a proximal low-pressure occlusion balloon catheter (Helios™, LightLab Imaging, Inc.) and an OCT system console on a mobile cart that contains the optical imaging engine and computer for signal acquisition (M2/M3 CV OCT Imaging System, LightLab Imaging, Inc.). The imaging probe contains an optical fiber with a microlens assembly at its tip. To obtain a single cross-section OCT image, the optical fiber rotates within a stationary transparent protective sheath, scanning the OCT beam around the circumference of the vessel. An automatic pullback mechanism pulls the fiber back longitudinally with the vessel at 1–3 mm/s to obtain a series of cross-sectional images within a vessel segment.

In contrast to TD-OCT, which uses a broadband light source, the FD-OCT, uses a laser that emits near monochromatic light within an optical frequency that sweeps rapidly over a broad wavelength range. This rapid variation in the optical frequency makes it possible to obtain...
Pullback rate (mm/s) 20
Resolution (mm) 10–20
Modalities Frequency-domain optical coherence tomography Intravascular ultrasound
Tissue penetration (mm) 1.0–2.5 10
Maximum scan diameter (mm) 10 15

Table 1. Optic- and ultrasound-based imaging modalities.

100 frames of data each second, while fewer than ten frames per second can be obtained at the same line density with a conventional TD-OCT system. Hence, FD-OCT increases the speed of data acquisition markedly and enables scanning of longer segments of the coronary arteries during a single flush. Takarada et al. reported that FD-OCT yielded a higher rate of clear images compared with TD-OCT without ischemic ECG changes in the clinical setting [1]. Better feasibility and performance with procedural safety of FD-OCT can overcome several limitations of conventional TD-OCT systems and facilitate practical application of OCT in the clinic, such as assessment of coronary lesion morphology, guidance for percutaneous coronary intervention (PCI) and long-term evaluation of the lesion treated.

The first commercial FD-OCT system, developed by LightLab Imaging, Inc., consists of an OCT imaging catheter (C7 Dragonfly™) and an OCT system console (C7 XRTM™). Other companies have announced plans to introduce FD-OCT systems in the coming years.

Intravascular ultrasound versus OCT
Since IVUS was first developed in the early 1990s, it has been widely used for the assessment of coronary artery morphology and the optimization of PCI [2]. IVUS provides useful information regarding vessel size, plaque area and morphology for stent implantation. However, the resolution of IVUS (100–150 µm), limits the ability of IVUS to detect detailed structures such as intimal tears, thrombus, stent malapposition and tissue prolapse during stent implantation. By contrast, the high resolution of OCT allows visualization of fine coronary structures. This new imaging modality may be useful not only for detecting different types of coronary plaque (lipid-rich, fibrous and calcified plaques) [2–4], but also for facilitating PCI procedures with visualization of intimal hyperplasia, intimal tears and intraluminal thrombi before PCI, and stent malapposition, strut distribution, stent edge dissection, tissue prolapse and mural thrombus after PCI [5–8]. However, in several applications, the shallower penetration of OCT may be a drawback (Table 1). Whole vessel structures, including the external elastic lamina, cannot be visualized consistently by OCT, especially through lesions with a high amount of lipid-rich plaque burden.

Assessment of coronary lesions with OCT

Plaque characterization
Tissue characterization of atherosclerotic plaques with OCT was first carried out by comparing the OCT images to the matched histology using autopsy specimens [2]. Each of the three major plaque types is characterized by a specific set of features: fibrous plaques appear as homogeneous, signal-rich regions; lipid plaques as signal-poor regions with diffused borders; and calcified plaques as signal-poor regions with sharp borders (Figure 1). Lipid pools are less sharply delineated than calcifications and show lower signal intensity. Lipids also exhibit more homogeneous backscattering than fibrous plaques. OCT can also identify thin-cap fibroatheroma by measuring the thickness of the fibrous cap and the arc of lipid-rich plaque [3,9,10]. Thrombi are defined as protruding masses into the lumen that are discontinuous from the surface of the vessel wall, with a variable degree of OCT signal attenuation behind the mass (Figure 2) [3,9,10]. OCT images for red thrombi, which mainly consist of red blood cells, are characterized as high backscattering protrusions with strong signal attenuation. White thrombi, which consist mainly of platelets and white blood cells, are characterized by a signal-rich protruding mass [11]. Plaque ulceration or rupture can be visualized by OCT as a ruptured fibrous cap that connects the lumen with the lipid pool. Thrombi are frequently found in the culprit lesion of patients with acute coronary syndrome (ACS). A large amount of red thrombus may interrupt the visualization underneath plaque morphologies owing to signal attenuation. Tänaka et al. reported the frequency of no-reflow phenomena after PCI according to the lipid arc and related their findings with the frequency of thin-cap fibroatheroma in patients who present with non-ST-elevation ACS [10]. OCT may have the potential to detect high-risk coronary plaques for early intervention strategies in ACS patients [10]. Figure 3 shows an example of an OCT image of a lesion that exhibited no-reflow after stent placement. Mural red thrombi are possibly misdiagnosed as lipid-rich fibroatheroma, mainly owing to similar OCT signal attenuation patterns of the plaque components.
Careful examinations assessing surface continuity and structure are needed to differentiate mural red thrombi and lipid-rich fibroatheroma.

### Vessel sizing with OCT

Optical coherence tomography can provide cross-sectional images with clear delineation between the coronary lumen and vessel wall, although the shallow penetration of OCT may limit the visualization of whole-vessel structure when compared with IVUS. Yamaguchi et al. reported that the minimal lumen area and diameter measured on OCT images correlated well with those measured on IVUS images [12]. OCT can also provide accurate measurements of reference lumen diameters when applied to pre-PCI lesion evaluation (Figure 3). Kawamori et al. reported that lumen diameters at the proximal site of culprit lesions measured on TD-OCT images were almost identical to those measured with IVUS. However, the lumen diameter at the distal site of the culprit lesions on OCT images was smaller than that measured on IVUS images. This may be related to a decrease in intracoronary pressure during OCT imaging resulting from proximal vessel occlusion with a balloon [13]. Image acquisition without vessel occlusion by FD-OCT systems may be more convenient and effective for measurement of vessel size and estimation of the proper size of the coronary stent [1].

### Definition of percutaneous coronary intervention end points with OCT

Optical coherence tomography is useful for the evaluation of stent expansion and strut apposition to vessel wall immediately after stent deployment. Since OCT light cannot penetrate into the metal struts of the stent, the luminal surface shows a strong reflection with shadowing behind the struts (Figure 4A). Stent diameter and area postimplant can be measured accurately by OCT, with results nearly identical to those obtained by IVUS [14]. The stent area measured by OCT imaging could possibly be an alternative end point of PCI. Bouma et al. reported that dissection, prolapse and incomplete stent apposition were observed more frequently with OCT than with IVUS [5,13]. Figure 4 shows examples of OCT images immediately after stent deployment in a coronary lesion. Edge dissection after stent implantation is clearly visualized by OCT; a fraction of these could become occlusive over time and need additional stenting. Tissue prolapse also can be detected in most of the cases of post-stent implant by OCT [5,12]. Although minor tissue prolapse and thrombus formation may be spontaneously resolved within 1 month, it is still controversial which of these can be safely left without additional treatment and those that should be treated with additional balloon dilation. The lesion morphologies before and after coronary stenting and serial changes might be different between patients with stable angina pectoris and ACS. One study from Kubo et al., suggested that although the inadequate lesion...
that uncovered struts could be a marker of the lack of re-endothelialization, which correlates with stent thrombosis [19]. In vivo assessment of strut coverage emerged as an important surrogate for risk stratification of stent thrombosis. According to IVUS examinations, most DES appear uncovered by neointima at a chronic stage; however, the limited resolution of IVUS makes it difficult to evaluate the extent or thickness of neointimal coverage. Using OCT, strut coverage with neointima is clearly visible and both the conditions of the coverage of individual struts and the thickness of neointimal coverage can be evaluated [7]. Classification of strut coverage is illustrated in Figure 5.

Matsumoto et al. reported that at 6-month follow-up, 89% of the sirolimus-eluting stents (SES) lesions were covered by thin neointima, and that 64% of the stent struts were covered with neointima that had a thickness of less than 100 µm, which is undetectable by IVUS. Most of the SES lesions appeared to be covered by thin neointima, but the frequency of fully covered SES was only 16% at 6 months. Therefore, according to this study, most SES have partial uncovered struts at 6 months [7].
Katoh et al. performed serial OCT follow-up of the same patients and reported a comparison of OCT findings at 6 months and at 12 months in identical SES. The neointimal thickness increased from 112 ± 123 µm to 120 ± 130 µm and frequency of uncovered struts decreased from 10.4 to 5.7% [8]. This indicates that SES undergoes long-term delayed neointimalization. An important unanswered question has emerged: when do most SES become fully covered by neointima? There is a possibility that partially uncovered struts remain long term, perhaps for more than 5 years in SES [20].

Another question is whether the uncovered struts are thrombogenic or not. Otake et al. reported that the frequency of mural thrombus detected by OCT in SES was 26% (14/53 lesions) at 6 months and subclinical thrombus was associated with a larger number of uncovered struts, uneven neointimal thickness, larger stent eccentricity and longer SES [21]. This suggests uncovered stent struts may be thrombogenic and mural thrombus in SES does not seem to be a rare phenomenon.

A contrary suggestion has been made by Murakami et al. that strut coverage with neointima on DES may not always prevent thrombus formation [22]. An important question remains about whether the tissue covering DES is antithrombogenic. According to pathologic studies, tissue covering DES may not always consist of endothelium containing smooth muscle cells, but may contain fibrin, proteoglycan or inflammatory cells [19]. According to our OCT studies, neointima covering DES often does not appear homogeneous in OCT images (Figure 6). The inhomogeneous regions in OCT images are likely to be related to atypical tissue growth in the neointima. As yet, there have been few comparison studies between OCT images of stent coverage and histopathology, due to the limited availability of autopsy samples. More extensive histological studies are needed to clarify these issues.

Figure 4. Examples of optical coherence tomography images post-stent deployment. (A) Stent with full round-shape expansion and complete apposition to the vessel wall. (B) Struts malapposed to the vessel wall (arrow head). (C) Tissue prolapse between the stent struts (arrow head). (D) Thrombus formation after stent deployment (arrow head). (E) Struts penetrating into the original thrombi within the lesion (arrow head). (F) Dissection of the native coronary wall at the distal edge of the stent (arrow head).

Assessment of stent restenosis with OCT

Restenosis caused by exaggerated neointimal proliferation was the main limitation for the long-term success of BMS. In the recent DES era, although its incidence has been dramatically reduced, restenosis still occurs and its pathophysiology is poorly understood. According to our observations, OCT images of stent restenosis are not homogeneous. Restenotic tissue growth evaluated by OCT can be categorized into three main patterns: homogenous, layered and heterogeneous (Figure 7). According to our data, the homogeneous pattern was observed in all BMS restenosis cases, in contrast to SES restenosis whereby 13% were...
classified as homogenous, 74% as layered and 13% as heterogeneous. In paclitaxel-eluting stent restenosis, 29% were classified as homogenous, 42% as layered and 29% as heterogeneous [23]. Gonzalo et al. reported a similar classification of restenotic tissue patterns assessed by OCT, including in different kinds of DES and BMS [24]. Neointimal tissue growth and its pathological tissue characteristics are expected to depend on the type of drug, coating and polymers on DES, as well as the original plaque composition of the stented lesion and the elapsed time after stent implantation.

Figure 5. Optical coherence tomography classification of strut conditions at the chronic phase post-stent implant. (A) Well apposed with neointima, (B) well apposed without neointima, (C) malapposed with neointima, (D) malapposed without neointima, (E) side branch orifice with coverage and (F) side branch orifice without coverage. Classification reproduced from [7].

Figure 6. Different morphological types of neointima at 6 months after sirolimus-eluting stent and paclitaxel-eluting stent implantation. Although all stent struts are considered to be covered, optical coherence tomography signal intensity and texture patterns are various. (A) Protruding struts with tissue attachment, (B) neointimal with peristrut low-signal area (arrow head), (C) homogeneous high-signal neointima, (D) layered neointima of homogeneous high- and low-signal area (arrow heads), (E) heterogeneous low-signal neointima, (F) neointimal with peristrut low-signal area (arrow head), (G) homogeneous high-signal neointima and (H) heterogeneous low-signal neointima, including multiple speckled spots. PES: Paclitaxel-eluting stent; SES: Sirolimus-eluting stent.
Future progress in OCT tissue characterization will enable us to address pathological neointimal features in this unknown entity.

**OCT observations of very late stent thrombosis after DES implant**

As previously mentioned, subclinical thrombus formation is not rare in the current generation of DESs. However, in the study by Otake et al., none of the cases suffered major adverse cardiac events in follow-up (up to 485 days) [21]. The mechanisms leading to very LST are complex and incompletely understood. Delayed arterial healing and incomplete re-endothelialization have emerged as the prevailing mechanism of thrombosis in autopsy studies [19]. Cook et al. demonstrated that very late DES thrombosis is associated with histopathological signs of inflammation and IVUS evidence of vessel remodeling, which correlates with the extent of stent malposition [25]. Sawada et al. reported OCT observations of very LST 29 months after SES implant. IVUS presented positive arterial remodeling at SES-implanted sites and OCT revealed multiple interstrut ulcer-like appearances and late strut malappositions (Figure 8) [26]. These might be OCT signs of a critical situation for very LST, which can be detected by OCT follow-up examination for current-generation DES. Hopefully, newer generations of DES will attempt to address these concerns by aiming to improve vascular healing while maintaining potent neointimal suppression.

**Conclusion**

Optical coherence tomography provides new insights into the assessment of coronary artery disease. The high resolution of OCT enables detailed evaluation of coronary atherosclerosis; fibrous plaques, lipid-rich plaques with thin fibrous caps, dense calcified lesions and angiographically hazy stenosis containing thrombus can be accurately visualized.
identified. Furthermore, vascular response to coronary intervention such as stent expansion, tissue prolapse within the stent and thrombus formation can be clearly visualized. OCT can also measure the thickness of neointima and strut conditions at follow-up examination, which may help to stratify the risk of thrombotic events associated with DES.

Future perspective
Penetration depth of OCT is limited to approximately 2 mm, either by TD-OCT or FD-OCT. Thus, although the current OCT system can visualize thin fibrous caps of fibroatheroma and thin neointimal coverage on DES, it is unable to quantify whole vascular structures and total plaque volume, which can be surrogates in response to specific treatments aimed at regression or cessation of progression. Development of new devices equipped with both IVUS and OCT functions should be helpful for patient evaluation and large clinical trials.

At present, standard OCT interpretation is limited to the evaluation of grayscale images generated by near-infrared light reflections at tissue interfaces and the identification of individual plaque components by OCT requires experience. The application of postprocessing color-mapping software based on OCT light backscatter and attenuation should improve the characterization of both atherosclerotic coronary plaques and neointimal tissue on DES by providing more objective assessment [27].

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Executive summary

- Optical coherence tomography (OCT) is an imaging modality based on fiberoptic technology that provides high resolution (~ten-times higher than that of intravascular ultrasound) and real-time intracoronary images. OCT enables us to characterize plaque types, such as fibrous, calcified and lipid plaques. OCT can also identify thin-cap fibroatheroma by measuring the thickness of the fibrous cap and the arc of lipid-rich plaques.
- OCT is superior to intravascular ultrasound in detecting detailed structures, such as intimal tears, dissections, thrombus, stent apposition and incomplete apposition and tissue prolapse during stent implantation, which may facilitate percutaneous coronary intervention procedures.
- OCT is useful for the evaluation of vascular healing after drug-eluting stent implantation in assessing neointimal coverage, incomplete stent apposition and thrombus formation.
- Frequency-domain OCT will overcome several limitations of time-domain OCT. In the near future, frequency-domain OCT is expected to be adopted extensively in clinical use.

Bibliography

Papers of special note have been highlighted as:

28 Quantitative assessment of optical properties of plaque tissue.