Optical Coherence Tomography for Study of *In Vivo* Pathobiology and for Optimization of Percutaneous Coronary Intervention

Tomoyo Sugiyama, MD, PhD,¹ Ik-Kyung Jang, MD, PhD^{1,2*}

¹Cardiology Division, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

²Division of Cardiology, Kyung Hee University Hospital, Seoul, Republic of Korea

Intravascular optical coherence tomography (OCT) is an imaging modality uniquely characterized by its high resolution. OCT can visualize *in vivo* plaque characteristics and detect vulnerable plaque, such as thin-cap fibroatheroma, which has a large lipid pool with overlying thin fibrous cap. OCT can also help the clinicians to identify the underlying pathology of acute coronary syndrome: plaque rupture, plaque erosion, and calcified nodule. The OCT system enables automated measurement of the lumen diameter, lumen area, and lesion length, which is useful to determine appropriate reference sites, stent size and stent length during percutaneous coronary intervention (PCI). Evaluation of underlying plaque characteristics is helpful in predicting possible complications after PCI. OCT-guided PCI may acquire comparable angiographical and clinical outcomes to intravascular ultrasound-guided PCI. OCT can be used to evaluate characteristics of non-culprit plaque and efficacy of lipid-lowering therapy on plaque stabilization. OCT also clearly visualizes mechanical vessel injury after stent implantation. Notably, the presence of irregular tissue protrusion has been shown to be associated with the occurrence of device-oriented clinical events. Recent studies suggest that OCT is feasible for the selection of conservative management without stenting in patients with acute coronary syndrome caused by plaque erosion.

Key words: optical coherence tomography, percutaneous coronary intervention

Introduction

It has been 40 years since the first balloon coronary angioplasty procedure was performed.¹⁾ Since then, development of treatment devices such as bare metal stents,²⁾ drug-eluting stents,³⁾ and bioresorbable vascular scaffolds⁴⁾ has dramatically changed the management of patients with coronary artery disease. Intracoronary imaging modalities such as intravascular ultrasound (IVUS), developed in the late 1980s and utilized in clinical practice since the 1990s,^{5–8)} and coronary angioscopy (CAS), developed in the early 1990s,^{9–11)} have been used to enrich our understanding of *in vivo* pathology of coronary atherosclerosis as well as to improve the outcomes of percutaneous coronary intervention (PCI). Optical coherence tomography (OCT) was first developed for *ex vivo* imaging of the atherosclerotic plaque in the

1990s.^{12–14)} After *ex vivo* validation by autopsy specimen,¹⁵⁾ the first-in-man study was conducted at the Massachusetts General Hospital to evaluate the feasibility of OCT to visualize plaque components in the coronary arteries.¹⁶⁾ The first-generation time-domain OCT became commercially available in 2002. The second-generation frequency-domain (Fourier-domain) OCT was introduced in 2010 with occlusion-free imaging, improved pull-back speed with higher frame rate, and increased axial scan density for improved image quality. The latest model of OCT (C8 ILUMIEN OPTIS PCI Optimization System, St. Jude Medical, Inc., St. Paul, MN, USA) provides imaging with a faster pull-back speed of 18–36 mm/s (180 frames/s), greater pull-back length of 54–75 mm, and real-time three-dimensional image reconstruction.

In Vivo Plaque Characterization

The strength of OCT imaging is its high resolution (10–20 μm),¹⁷⁾ which has enabled visualization of coronary artery structures and plaque characteristics such as fibrous, fibrocalcific, and lipid-rich plaques (Fig. 1),¹⁵⁾ and established the measurement of

* 55 Fruit Street GRB 800, Boston, MA 02114, USA
Tel: +1-617-726-9226; Fax: +1-617-726-7416
e-mail: ijang@mgh.harvard.edu
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Fig. 1 Plaque characterization by optical coherence tomography.

- (A) Normal coronary artery wall consists of three layers: intima, media, and adventitia.
- (B) Fibrous plaque is characterized by a homogenous, signal-rich region.
- (C) Fibrocalcific plaque shows well-delineated, signal-poor regions with sharp borders (asterisk).
- (D) Lipid-rich plaque is characterized by signal-poor lipid pool with diffuse borders (arrow head) with an overlying fibrous cap (arrow).

fibrous cap overlying lipid-rich plaques.¹⁸⁾ OCT has also enabled *in vivo* detection of vulnerable plaques such as thin-cap fibro-atheromas (TCFA), defined as plaques with large lipid pool and overlying thin fibrous cap,¹⁹⁾ that are prone to rupture and suggestive of plaque vulnerability.²⁰⁾ Fibrous cap thickness on OCT is correlated to CAS-derived yellow grade of plaque,²¹⁾ which suggests large lipid pool on histological examination.²²⁾ OCT is the only intravascular imaging modality able to visualize coexisting features of plaque instability such as macrophage accumulation,²³⁾ microvessel,²⁴⁾ and cholesterol crystals.^{19, 25)} OCT can also detect intraluminal thrombus and classify its components into white (platelet-rich) thrombus and red (erythrocyte-rich) thrombus based on material structure and signal intensity attenuation.^{26, 27)}

Detection of Culprit Plaque Morphologies in Acute Coronary Syndrome

Pathology reports have shown that there are three major underlying mechanisms for acute coronary thrombosis contributing to acute coronary syndrome (ACS) and sudden cardiac death: plaque rupture, plaque erosion, and calcified nodule (Fig. 2).^{20, 28)} OCT is feasible to detect culprit plaque morphologies in patients with ACS.²⁹⁾ The most frequent etiology of ACS is plaque rupture (Fig. 2A). OCT can clearly visualize plaque ruptures as fibrous cap discontinuity with cavity formation.^{19, 29)} The incidence of plaque rupture is mainly determined by fibrous cap thickness, and a combination of large plaque burden and luminal narrowing leads to plaque rupture in patients with ACS.³⁰⁾ Plaque rupture is more frequently observed in culprit plaques of patients with ST-segment-elevation myocardial infarction

(STEMI) compared to those with non-ST-segment-elevation acute coronary syndrome (NSTEMI-ACS).³¹⁾ Patients with plaque rupture have greater pancoronary vulnerability and systemic inflammation.^{32, 33)}

OCT has also allowed *in vivo* diagnosis of plaque erosion (Fig. 2B).³⁴⁾ Despite its high resolution, current OCT system cannot image the detachment of endothelial cells.³⁵⁾ OCT-erosion has been classified based on the absence of fibrous cap disruption and the presence of thrombus: definite OCT-erosion identified by the presence of attached thrombus overlying an intact and visualized plaque; and probable OCT-erosion defined by i) luminal surface irregularity at the culprit lesion in the absence of thrombus; or ii) attenuation of underlying plaque by thrombus without superficial lipid or calcification immediately proximal or distal to the site of thrombus.³⁴⁾ There have been no distinct morphological features identified as precursors of plaque erosion.³⁶⁾

OCT-derived calcified nodule (Fig. 2C) has been defined as fibrous cap disruption over calcified plaque with thrombus attachment, which is characterized by protruding calcification, superficial calcium, and the presence of substantive calcium proximal and/or distal to the lesion.³⁴⁾ Thus far, no systematic study of OCT-derived calcified nodules has been published.

There are several other causes of ACS. Spontaneous coronary artery dissection can be clearly visualized with the appearance of double-lumen (true and false lumens) or intramural hematoma.³⁷⁾ OCT may help to make stenting approach possible such as sealing the intimal tear to close the entry of dissection.³⁸⁾ Coronary spasm-induced ACS is commonly accompanied by intraluminal thrombus and erosion on OCT,^{39, 40)} but it remains un-

Fig. 2 Representative images of culprit plaque morphologies of acute coronary syndrome on optical coherence tomography (OCT) (upper row) and coronary angioscopy (CAS) (lower row). Figure courtesy of Dr. Shigeki Kimura.

- (A) Plaque rupture is characterized by fibrous cap discontinuity with cavity formation (asterisk) on OCT and fibrous cap disruption protruding into the lumen (arrow) on CAS.
- (B) Plaque erosion is identified by the presence of attached thrombus overlying an intact and visualized plaque on OCT, or if the plaque shows surface erosion with no evidence of disrupted fibrous cap protruding into the lumen on CAS (white arrowhead).
- (C) Calcified nodule is defined as fibrous cap disruption over calcified plaque on OCT. In this case, CAS indicates light yellow mass on the surface (black arrowhead).

certain whether repeated spasm may cause plaque erosion or vice versa.

OCT Guidance for PCI

OCT system enables automated measurement of the lumen diameter and lumen area in each cross-sectional frame, and lesion length by the longitudinal view. These measurements are useful to determine appropriate reference sites, stent size, and stent length during PCI. The presence of lipidic plaque and fibrocalcific plaque at the stent edge is associated with the higher incidence of stent edge dissection than fibrous plaques.^{41, 42)} The presence of lipidic plaque at the stent edge is also reportedly associated with post-PCI myocardial infarction⁴³⁾ and stent edge restenosis.⁴⁴⁾ Therefore, selecting healthy landing zones is preferred for optimal stent deployment.⁴⁵⁾

The evaluation of underlying plaque characteristics is also important to predict worse outcomes after PCI. The presence of OCT-derived TCFA is associated with the occurrence of no-reflow phenomenon,⁴⁶⁾ post-PCI myocardial injury/infarction,^{47–49)} and microvascular obstruction on cardiac magnetic resonance imaging.⁵⁰⁾ Greater amount of residual thrombus burden after aspiration thrombectomy is related to worse microvascular dys-

function and greater post-PCI myocardial injury.⁵¹⁾

Usefulness of OCT guidance for PCI has been evaluated in several studies. In the retrospective CLI-OPCI study, OCT-guided PCI was associated with a significantly lower one-year risk of the composite of cardiac death, myocardial infarction, or repeat revascularization compared to angiography-guided PCI.⁵²⁾ In the ILUMIEN I study, PCI optimization based on pre-PCI and post-PCI OCT was associated with reduced rates of post-PCI myocardial infarction.⁵³⁾ The ILUMIEN II study reported OCT guidance was associated with comparable stent expansion to IVUS guidance.⁵⁴⁾ The DOCTORS study demonstrated that OCT-guided PCI was associated with higher post-PCI fractional flow reserve than angiography-guided PCI.⁵⁵⁾ The OPINION trial demonstrated non-inferiority of optical frequency-domain imaging-guided PCI compared to IVUS-guided PCI with regard to the incidence of target vessel failure for 1 year⁵⁶⁾ and the acquisition of comparable minimal lumen area at 8-month follow-up OCT.⁵⁷⁾ The ILUMIEN III: OPTIMIZE PCI study was the first randomized controlled trial that compared OCT-guided, IVUS-guided, and angiography-guided PCI. In this study, OCT guidance showed similar angiographical and clinical outcomes, and non-inferiority in achieving similar minimal stent area,

compared to IVUS guidance.⁵⁸⁾ Larger randomized controlled trials are warranted to evaluate whether OCT-guided PCI yields superior outcomes to IVUS-guided or angiography-guided PCI.

Evaluation of Non-culprit Plaque Characteristics

OCT has an advantage in evaluating the characteristics in non-culprit plaques. The greater vulnerability in non-culprit plaques is observed in patients with ACS,⁵⁹⁾ diabetes mellitus,^{60, 61)} and chronic kidney disease.⁶²⁾ A recent study showed that the presence of non-culprit lipid-rich plaque in PCI-treated vessels was associated with non-culprit lesion-related future events.⁶³⁾ These studies suggest that OCT can identify patients at high risk in the future.⁶⁴⁾ Efficacy of medical therapy can be also evaluated by OCT. More intensive lipid-lowering therapy with statins has been associated with an increase in fibrous cap thickness and decrease in lipid arc in non-culprit plaques, which may lead to plaque stabilization.⁶⁵⁻⁶⁷⁾

Post-stent OCT Findings on Outcomes after PCI

IVUS-guided PCI has been shown to reduce major adverse cardiac events (MACE) including target lesion revascularization and stent thrombosis in the era of second-generation drug-eluting stents (DES).⁶⁸⁾ On the other hand, attempts to show the strength of OCT-guided PCI over IVUS-guided PCI on long-term outcomes have not been successful. Suboptimal stent deployment with unsatisfactory minimal stent area on OCT is associated with increased risk of MACE.⁶⁹⁾ OCT clearly and sensitively visualizes mechanical vessel injury after stent implantation such as stent edge dissection, incomplete stent apposition, and tissue protrusion^{70, 71)} in higher frequency compared to

IVUS.^{72, 73)} OCT is capable of detecting smaller stent edge dissection (Fig. 3A) than IVUS,⁷⁴⁾ but OCT-detected stent edge dissection is not associated with the clinical events.⁷³⁻⁷⁷⁾ Incomplete stent apposition (Fig. 3B) may be related to persistent malapposition,⁷⁵⁾ or delayed neointimal coverage,⁷⁸⁾ but small incomplete stent apposition is not related to clinical events.^{73-76, 79)} Tissue protrusion (Fig. 3C) may be related to neointimal hyperplasia,⁸⁰⁾ but does not affect the occurrence of clinical events either.^{72-76, 80-82)} Notably, the presence of irregular tissue protrusion, which suggests deep vessel injury and underlying large lipid components, has been shown to be associated with the occurrence of device-oriented clinical events for 1 year.^{76, 83)} So far, the way to prevent the incidence of irregular tissue protrusion or to treat irregular protrusion after PCI remains undetermined.

Tailored Management in Patients with Plaque Erosion

Currently, patients with ACS have been uniformly treated with stent implantation.^{84, 85)} Recent studies suggest that conservative management without stenting may be an option in patients with ACS caused by plaque erosion.^{86, 87)} OCT is the only intracoronary imaging device that can visualize plaque erosion owing to its high resolution. The EROSION study has shown the feasibility and safety of anti-thrombotic therapy without stenting in patients with ACS caused by plaque erosion.⁸⁶⁾ The use of OCT may bring a major shift in the management away from routine stenting toward more tailored management in patients with plaque erosion.

Fig. 3 Post-stent findings on optical coherence tomography (OCT).

- (A) Stent edge dissection is defined as disruption of the vessel luminal surface with a visible flap (arrow) at the stent edge.
- (B) Incomplete stent apposition is defined as separation of the inner surface of a stent strut from the inner vessel wall (broken circle) by a distance greater than or equal to the axial resolution of OCT plus the width of the stent strut.
- (C) Tissue protrusion. In this case, irregular protrusion is identified by the presence of protrusion of material with an irregular surface into the lumen between the stent struts.

Limitations and Future Directions of OCT

To date, OCT-guided PCI has not been shown to be superior to IVUS-guided or angiography-guided PCI regarding long-term outcomes. The planned ILUMIEN IV study will be expected to evaluate long-term outcomes in patients randomized to OCT-guided PCI versus angiography-guided PCI. Advance in technology is remarkable in this field. Micro-OCT is capable of visualizing cellular and subcellular features such as macrophages and endothelial cells with 1- μ m resolution, which may enable more accurate diagnosis of plaque erosion.⁸⁸⁾ Catheter-based micro-OCT imaging is on the horizon.⁸⁹⁾ Hybrid intravascular imaging modalities are being developed. Combined OCT-IVUS enables more accurate assessment of plaque composition and structure.⁹⁰⁾ OCT-near infrared fluorescence imaging can image and quantify plaque inflammation.⁹¹⁾ OCT-near infrared autofluorescence imaging⁹²⁾ and OCT-near infrared spectroscopy imaging⁹³⁾ provide high-risk plaque composition such as necrotic core lipid. However, whether these new systems have clinical value needs to be tested.

Conclusions

OCT has been used as a great research tool for a better understanding of *in vivo* pathobiology of coronary atherosclerosis. In clinical settings, OCT guidance is useful for daily practices to evaluate plaque characteristics of culprit and non-culprit lesions, optimize PCI procedures, and predict future events. OCT may also contribute to the selection of tailored management and treatment strategy depending on the etiology of ACS, especially plaque erosion. It is expected that the clinical value of OCT will be established when upcoming clinical trials demonstrate the superiority of OCT-guided PCI over angiography-guided PCI.

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