Stent Evaluation with Optical Coherence Tomography

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Optical coherence tomography (OCT) has been recently applied to investigate coronary artery disease in interventional cardiology. Compared to intravascular ultrasound, OCT is able to visualize various vascular structures more clearly with higher resolution. Several validation studies have shown that OCT is more accurate in evaluating neointimal tissue after coronary stent implantation than intravascular ultrasound. Novel findings on OCT evaluation include the detection of strut coverage and the characterization of neointimal tissue in an *in-vivo* setting. In a previous study, neointimal healing of stent strut was pathologically the most important factor associated with stent thrombosis, a fatal complication, in patients treated with drug-eluting stent (DES). Recently, OCT-defined coverage of a stent strut was proposed to be related with clinical safety in DES-treated patients. Neoatherosclerosis is an atheromatous change of neointimal tissue within the stented segment. Clinical studies using OCT revealed neoatherosclerosis contributed to late-phase luminal narrowing after stent implantation. Like *de novo* native coronary lesions, the clinical presentation of OCT-derived neoatherosclerosis varied from stable angina to acute coronary syndrome including late stent thrombosis. Thus, early identification of neoatherosclerosis with OCT may predict clinical deterioration in patients treated with coronary stent. Additionally, intravascular OCT evaluation provides additive information about the performance of coronary stent. In the near future, new advances in OCT technology will help reduce complications with stent therapy and accelerating in the study of interventional cardiology.

Key Words: Optical coherence tomography, stent, coronary artery disease

Although bare-metal stents (BMS) show better outcomes than balloon angioplasty in reducing acute vessel closure,[1,2] in-stent restenosis (ISR) of treated coronary arteries still remains a challenge. Pathologic studies have revealed that neointimal tissue within stented segments mainly consist of smooth muscle cells and extracellular matrix.[3,4] Thus, the inhibition of smooth muscle cell has been a therapeutic target of percutaneous coronary intervention for reducing overwhelming growth of neointimal tissue. Compared to BMS, drug-eluting stents (DES) show remarkably reduced rates of angiographic restenosis and improved clinical outcomes.[5,6] Therefore, DES, which comprises a metallic stent frame, anti-proliferative drugs and

polymer, has been the main agent for treating coronary artery disease until now. While DES is considered an ideal treatment modality for coronary artery disease, this benefit has been challenged with the emergence of stent thrombosis, a serious complication. According to recent registries, the rate of late stent thrombosis was 0.53% per year and steadily increased to 3% over 4 years in first-generation DES-treated patients.[7,8] Accordingly, balance between the efficacy and safety of DES should be considered in DES implantation in patients with coronary artery disease. As optical coherence tomography (OCT) has enabled the observation of delicate coronary vessels and stents with superior resolution, a number of OCT studies have investigated DES-treated lesions in various clinical situations. Therefore, we sought to review recent advances in OCT focusing on DES-treated lesions.

OCT VS. INTRAVASCULAR ULTRASOUND

Intravascular ultrasound (IVUS) has been the standard imaging modality for evaluating the status of a coronary stent. However, it is limited in evaluating neointimal tissue within the stented segment due to its low resolution. Contrary to IVUS, OCT has a resolution of 10-20 μm, which is about 10 times higher than that of IVUS (80-120 μm). Previous studies have shown the superiority of OCT over IVUS in relation to resolution capacity. Compared to IVUS, OCT showed better diagnostic accuracy for detecting a small degree of in-stent neointima, which was defined as occupying <30% of the stent area measured with histology.[9] The optical cutoff value of percent neointimal hyperplasia (NIH) cross-sectional area (CSA) for detecting NIH by IVUS was 14.7%; OCT-measured neointimal tissue of percent NIH CSA <14.7% cannot be detected with IVUS.[10]

Recently, time-domain OCT systems have evolved to next-generation frequency-domain OCT systems. In the former system, an occlusion balloon was inflated and lactated Ringer's solution was infused through a catheter for acquiring OCT images. However, the frequency-domain OCT system is able to generate frames at much higher rates and allows for faster pullback speeds. Instead of the occlusion balloon, contrast medium is continuously flushed at a rate of 4 to 5 mL/s for 3 to 4 seconds. In an OCT study to evaluate the feasibility of frequency-domain OCT, frequency-domain OCT showed shorter procedural time (3.2±0.8

min vs. 11.2±2.5 min, p<0.01) and a higher acquisition rate of clear images (99.4% vs. 80.8%, p<0.01) than time-domain OCT.[11] Additionally, frequency-domain OCT was not related to any adverse cardiac events.[11] Frequency-domain OCT showed better detection of incomplete stent apposition (malapposition) or uncovered strut, compared with IVUS.[12,13]

STENT STRUT APPOSITION

In IVUS study, incomplete stent apposition is defined as a separation of at least one stent strut from the intimal surface of the arterial wall that is not overlapping a side branch and has evidence of blood flow behind the strut.[14] OCT enables one to observe apposition of a stent strut more accurately compared to IVUS; malapposed stent struts on OCT are defined as a distance between the strut marker and lumen contour greater than the strut thickness plus the axial resolution of OCT.[15] Accordingly, definitions of malapposed struts differ according to type of coronary stent because the thickness of struts and applied polymer vary. Fig. 1 shows typical examples of well-apposed and malapposed struts. The following are thresholds of malapposed struts for several DESs; ≥160 μm for sirolimus-eluting stent (Cypher Select™, Cordis, Miami Lake, FL, USA), ≥130 μm for paclitaxel-eluting stent (Taxus Liberte™, Boston Scientific, Natick, MA, USA), ≥110 μm for zotarolimus-eluting stent (Endeavor™ and Resolute™, Medtronic, Santa Rosa, CA, USA), ≥100 μm for everolimus-eluting stents (Xience™, Abbott Vascular, Santa Clara, CA, USA) and ≥130 μm for biolimus-eluting stent (Nobori™, Terumo Corporation, Tokyo, Japan or BioMatrix™, Biosensors Interventional, Singapore).[16-19]

As neointimal tissue proliferates after stent implantation, malapposed struts usually disappear when the distance between the stent strut and vessel wall is short.[16,20-22] Previous OCT study showed that the percentage of malapposed struts with minimal malapposition decreased from 12.2± 11.0% post-intervention to 1.0±2.2% after about 6 months of follow-up.[16] However, some struts are persistently malapposed after an index procedure (persistent malapposition) and some are newly detected at follow-up (late-acquired malapposition). Although the healing process of malapposed struts has not yet been clearly addressed, recent OCT studies showed incomplete stent apposition was more likely to be sustained as its distance (or area) was far
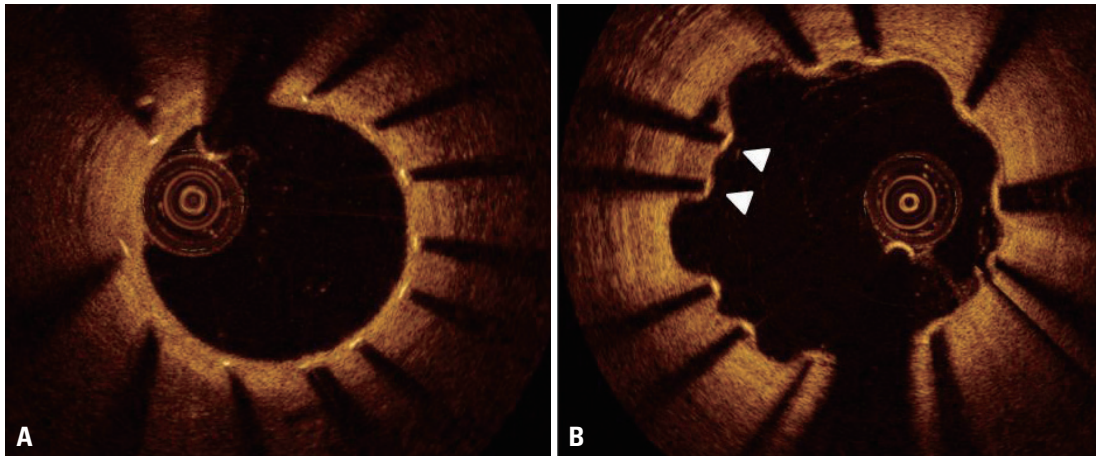
Fig. 1. Representative images of well-apposed vs. malapposed struts. Optical coherence tomography shows well-apposed struts with complete coverage 9 months after drug-eluting stent implantation (A), whereas some struts (arrowheads) show incomplete stent apposition and uncovered portions to the lumen (B).

from the vessel wall;[21,22] a strut-to-vessel distance of ≤260 μm on post-stenting OCT images was suggested as a cut-off value for resolved malapposition of first-generation DES.[22] Additionally, in other study, coverage of malapposed struts was delayed with respect to well-apposed strut at 9 to 13 months of follow-up after DES implantation.[23] Although overall malapposed struts were positively correlated with uncovered struts, a subgroup of lesions with minimal stent malapposition showed similar rates of uncovered struts to those without malapposition.[24] The coverage of malapposed struts was also affected by DES type, first- vs. new-generation DESs.[25]

STENT STRUT COVERAGE

A number of OCT studies have evaluated the *in-vivo* status of DES at various time points after stent implantation. According to these reports, the healing of DES was quite slow and heterogeneous even several years after stent implantation.[20,26,27] Neointimal growth after stent implantation is considered part of the wound healing process that generally occurs after injury.[3] This process generally consists of three phases: 1) an inflammatory phase (platelet aggregation and inflammatory cell infiltration), 2) a granulation phase (migration and proliferation of endothelial cells, fibroblasts or smooth muscle cells from adjacent tissue) and 3) a matrix remodeling phase (production of proteoglycan from fibroblasts and smooth muscle cells).[3] By these steps, BMSs are fully covered with neointima about 1 month after stent implantation.[3] Because anti-proliferative drugs with DES inhibits the migration and proliferation of smooth muscle cells,

delayed neointimal coverage of a DES is somewhat to be expected. However, even after the anti-proliferative drug is completely eluted into the adjacent wall, DES struts frequently remain uncovered upon *ex-* and *in-vivo* examination of implanted stents.[28-30] Few sirolimus-eluting stents show complete coverage at 6 months post-intervention.[29] For paclitaxel-eluting stents, another first-generation DES, one study also showed that the incidence of completely covered stents was 29.6% at 9 months post-intervention.[30] Consequently, patients treated with first-generation DES should receive dual anti-platelet therapy (aspirin and clopidogrel) for a longer time than those that received a BMS. To overcome the above limitation with first-generation DES, new-generation DESs have been developed with an advanced strut platform, polymer and new anti-proliferative drugs.

Table 1 summarizes the strut apposition and coverage of various DESs. Compared to sirolimus-eluting stent, the coverage of Endeavor zotarolimus-eluting stent was almost complete at 3 months.[31] The rate of stent thrombosis was 0.2% during 1-year follow-up in patients that received only 3-month dual anti-platelet therapy following Endeavor zotarolimus-eluting stent implantation in the REal Safety and Efficacy of 3-month dual antiplatelet Therapy (RESET) trial to evaluate the safety and efficacy thereof.[32] Resolute zotarolimus-eluting stent also showed higher rates of strut coverage than sirolimus-eluting stent at 9 months,[17] as did everolimus-eluting stent.[18] The Swedish Coronary Angiography and Angioplasty Registry (SCAAR) data revealed that the rates of restenosis and definite stent thrombosis in these new-generation DESs were lower than that of first-generation DESs.[33] Biolimus-eluting stent has the unique property of a biodegradable polymer with abluminal coat-

Table 1. Strut Apposition and Coverage of Drug-Eluting Stent Assessed by Optical Coherence Tomography

Study	Stent type	Follow-up (months)	Malapposed strut* (%)	Uncovered strut* (%)
Matsumoto, et al.[29]	Cypher™	6	1.2	11
Kim, et al.[30]	Cypher Select™ vs. Taxus Liberte™	9	2.6 vs. 1.5	12.5 vs. 4.9
Kim, et al.[56]	Endeavor Sprint™	3	0.2	0.1
Kim, et al.[31]	Endeavor Sprint™ vs. Cypher Select™	9	0.1 vs. 2.6	0.3 vs. 12.3
Kim, et al.[17]	Endeavor Resolute™ vs. Cypher™	9	0.1 vs. 1.5	4.4 vs. 10.3
Kim, et al.[57]	Endeavor Resolute™ vs. Xience V™	3	0.7 vs. 0.7	6.2 vs. 4.7
Gutiérrez-Chico, et al.[58]	Endeavor Resolute™ vs. Xience V™	13	1.8 vs. 1.4	7.4 vs. 5.8
Inoue, et al.[59]	Promus™	8	1.8	1.6
Takano, et al.[60]	Xience V™ or Promus™ vs. Taxus Express™	6	2.1 vs. 5.7	2.3 vs. 5.2
Choi, et al.[18]	Everolimus- vs. Sirolimus-eluting stent	9	0.4 vs. 1.7	4.4 vs. 10.5
Barlis, et al.[34]	BioMatrix Flex™ vs. Cypher Select™	9	0.2 vs. 0.4[†]	0.6 vs. 2.1[†]
Gutiérrez-Chico, et al.[19]	BioMatrix Flex™ vs. Cypher Select™	9	0.5 vs. 1.4[†]	2.8 vs. 5.7[†]
		24	0.1 vs. 0.4[†]	1.5 vs. 1.8[†]
Kim, et al.[61]	Cypher Select™	9 vs. 24	1.7 vs. 0.6	10.9 vs. 6.5
	Taxus Liberte™	9 vs. 24	1.0 vs. 0.3	4.0 vs. 3.7

*Values were presented as the percentage of strut which was divided by total number of analyzable struts.[15]
[†]Values were derived from Bayesian hierarchical models.
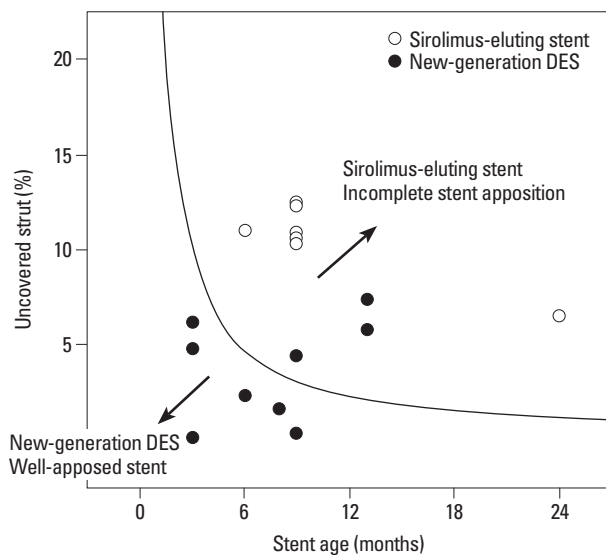

Fig. 2. Strut coverage of drug-eluting stent (DES) over time. A dot represents each of the studies in Table 1, except for Bayesian hierarchical models. A curved line represents estimated change of uncovered strut after DES implantation. Usage of sirolimus-eluting stent and incomplete stent apposition increases the risk of delayed coverage after DES implantation.

ing. In a sub-study of the Limus Eluted from A Durable vs. ERodable Stent coating (LEADERS) trial, OCT-defined coverage of biolimus-eluting stent was greater than that of sirolimus-eluting stent at 9 months.[34] The superiority of biolimus-eluting stent translated into greater clinical safety during 4-year follow-up; late definite stent thrombosis occurred less frequently in patients treated with biolimus-eluting stent.[35] Fig. 2 depicts various rates of DES coverage over time.

A recent autopsy study revealed delayed neointimal healing of implanted stent was associated with occurrence of late stent thrombosis; the odds ratio of a stent with a ratio of uncovered to total stent struts per section >30% was 9.0 (95% confidence interval, 3.5 to 22) for stent thrombosis.[28] In a case-control study in which OCT was performed at onset of stent thrombosis, the length of an uncovered stent strut segment was significantly associated with stent thrombosis.[36] Strut coverage assessed by OCT may be a surrogate marker for predicting catastrophic cardiovascular events in daily clinical practice. One OCT study suggested that a greater percentage of uncovered struts (a cut-off value of ≥5.9% uncovered struts), as assessed by OCT at 6-18 months follow-up, in asymptomatic DES-treated patients might predict increases in major adverse cardiac events related with stent safety in the future.[37]

In quantitative OCT analysis, stent and luminal CSA are measured, and NIH CSA is then calculated as the stent CSA minus the luminal CSA. Percentage of NIH CSA is calculated as NIH CSA×100/stent CSA. NIH thickness, the distance between the endoluminal surface of neointima and the strut, can be measured inside all struts as a line perpendicular to the neointima and strut.[38] An uncovered strut is defined as having a NIH thickness of 0 μm.[38] The percentage of malapposed or uncovered struts in each stented lesion can be calculated as the (number of malapposed or un-

covered struts/total number of struts in all cross-sections of the lesion)×100, respectively.

CHARACTERIZATION OF NEOINTIMAL TISSUE AND NEOATHEROSCLEROSIS

Because the NIH within stent segments mainly consists of smooth muscle cells and extra-cellular matrix, the predominant pattern of NIH by IVUS evaluation has been presented as a homogenous appearance.[10] However, one OCT study reported that various patterns of neointimal tissue develop in ISR lesions, suggesting that the mechanism for ISR might be complicated.[39] Fig. 3 shows homogeneous, heterogeneous and layered patterns of neointimal tissue. Differences in optical property and backscattering pattern arise from the heterogeneity of neointimal tissue, which contains various components such as fibrin accumulation, excessive inflammation (hypersensitivity reaction), extra-cellular matrix or in-stent neoatherosclerosis, as well as smooth muscle cells.[13] Therefore, it is difficult to conclude that specific types of neointimal tissue seen by OCT imply consistent histopathologic findings. Instead, observation of diverse neointima indicates that the healing process after stent deployment is not stable and may be associated with clinical events. An OCT study showed that heterogeneous or layered patterns of neointima were more frequently observed in ISR lesions than in non-ISR lesions.[40] However, to clarify the clinical implications of different neointimal features, further investigations are needed.

Neoatherosclerosis refers to an atherosclerotic change in neointimal tissue, which is histologically defined as clusters of lipid-laden foamy macrophages within the neointima with or without necrotic core formation.[41] On OCT images, lipidic neointima is shown as diffusely bordered, signal-poor regions with overlying signal-rich bands; calcific neointima shows well-delineated, signal-poor regions with sharp borders.[15,42] OCT-defined neoatherosclerosis is mainly confined to lipidic or calcific neointima.[43,44] Representative images of neoatherosclerosis are shown in Fig. 3. Neoatherosclerotic change in neointima occurs in both BMS and DES.[41,43] Previous histologic study found that neoatherosclerosis was observed more frequently and earlier in DES compared to BMS.[41] This finding was also shown in an OCT study,[43] suggesting incomplete endothelization might be involved in acceleration of atherogenesis inside neointima. Neoatherosclerosis contributes to late-phase luminal narrowing after stent implantation.[45,46] Previous angiographic study revealed that the luminal diameter of BMS followed a biphasic pattern of early narrowing and late improvement between 6 months and 3 years.[47] On the other hand, the neointima of DES continuously progressed up to 5 years.[48]
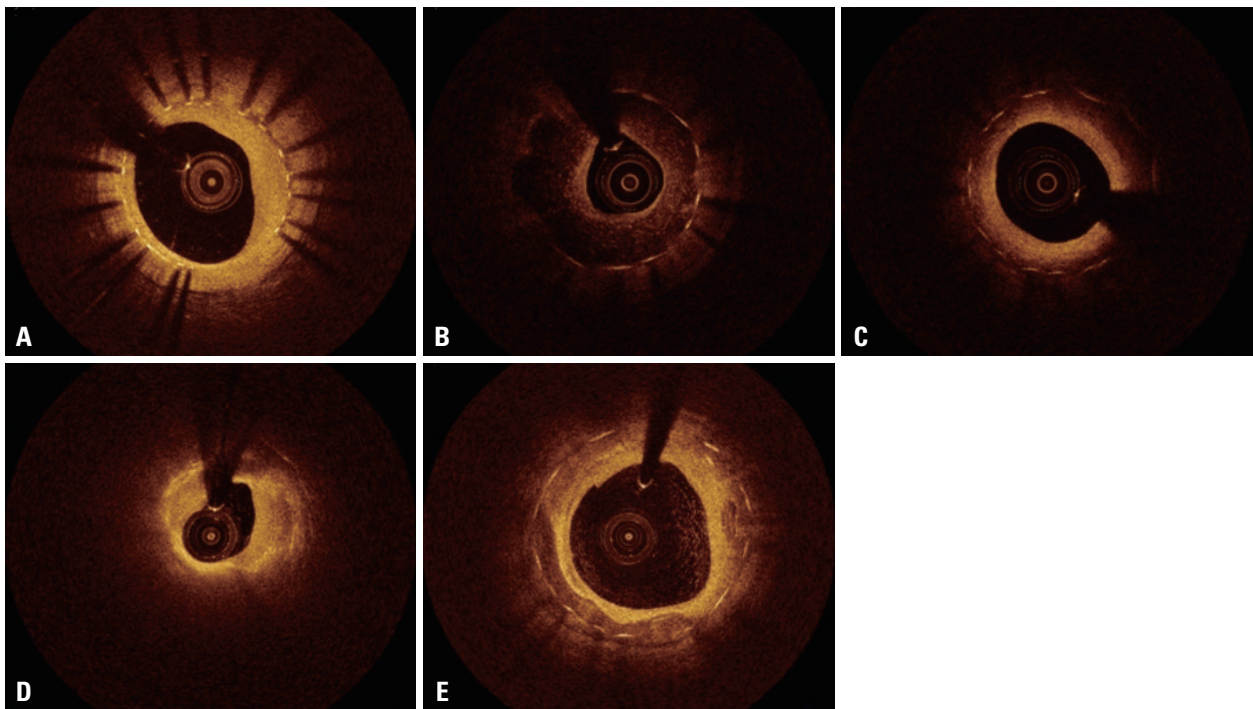

Fig. 3. Various patterns of neointimal tissue. (A) Homogeneous pattern, (B) heterogeneous pattern, (C) layered pattern, (D) lipid-laden neointima, (E) neointima with calcification.

An OCT study showed thin-cap fibroatheroma-like neointima was more commonly detected in very late ISR lesions (>3 years) than in early ISR lesions (<1 year).[46] Another serial OCT study also demonstrated that the frequency of neoatherosclerosis in DES-treated lesions increased between 9 months and 2 years.[26] Clinical presentation of neoatherosclerosis varies from stable angina to stent thrombosis. Compared to patients with stable angina, patients with unstable angina show higher incidences of OCT-defined thin-cap fibroatheroma, intimal rupture and thrombi.[49] In addition, OCT-defined rupture of lipidic neointima was observed in patients with very late stent thrombosis.[50] Although one OCT study suggested that risk factors of neoatherosclerosis were similar to those of native coronary artery disease,[44] the mechanism of neoatherosclerotic change remains unknown and needs to be investigated in the future.

LIMITATIONS

Although OCT is a recent advancement in intravascular imaging, a number of limitations remain. OCT has a shallow
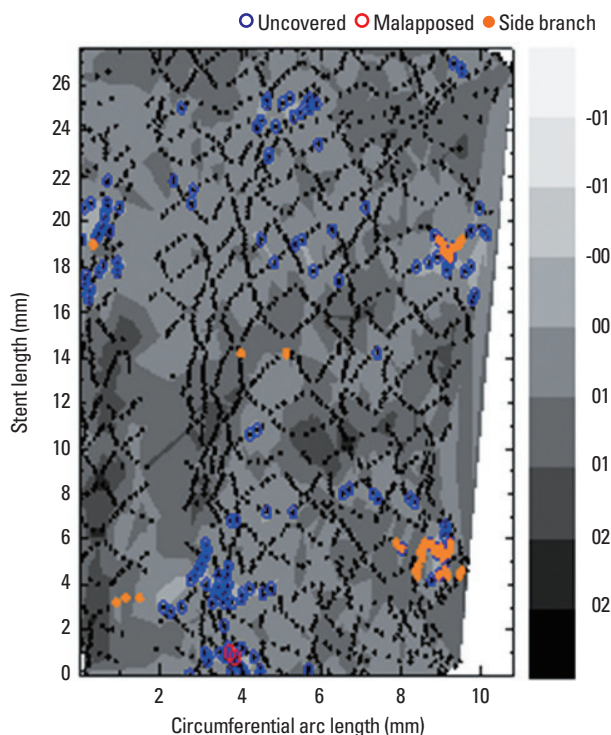

Fig. 4. Contour plot of strut coverage after drug-eluting stent implantation, using optical coherence tomography. The contour plot shows detailed information about the position and coverage of stent strut, in which the circumferential arc is plotted along the X axis and the stent length is plotted along the Y axis. Blue circles represent uncovered struts, red circles represent malapposed struts, and orange circles represent struts crossing over a side-branch vessel.[53]

penetration depth of about 2 mm and is not able to visualize structures behind severely attenuated components such as lipid-laden neointima or thrombus. In contrary to IVUS, blood in coronary arteries should be eliminated to acquire adequate OCT images because blood scatters light. For this purpose, continuous flush of saline or contrast media has been applied. Since frequency-domain OCT utilizes a faster authorized pullback system than time-domain OCT, it takes less time to inject contrast media. Nevertheless, it is inevitably necessary to create a blood-free field due to the natural limitation of optics. The current OCT system is not able to discriminate fibrin accumulation, excessive inflammation, abundant extracellular matrix, or neoatherosclerosis, because these are similarly shown as a dark appearance on OCT.[13,51]

FUTURE DIRECTIONS

Three-dimensional OCT technology is now under investigation for evaluating coronary artery disease. Three-dimensional OCT reconstruction allows researchers to analyze planes which are not visible on two-dimensional images.[52] Although three-dimensional OCT technology is still time-consuming, this application has been applied to the assessment of bifurcated lesion and coronary stent.[52,53] An OCT study showed that three-dimensional OCT reconstruction was feasible for evaluating the orifices of side-branch vessels after stent implantation.[52] Fig. 4 represents a contour map analysis for evaluating the status of a coronary stent strut.[53] By this approach, the performance of a coronary stent could be easily visualized at a glance. Tissue characterization with OCT remains a challenge because tissue components vary and some appear similarly on OCT. Several OCT techniques are being developed to enhance the differentiation of tissue components. Polarization-sensitive OCT is a novel technique that can be used to measure the polarization properties of backscattered light.[54] Cellular targeting agents such as fluorophores may be useful to characterize neointimal tissues, combined with hybrid OCT systems.[55]

CONCLUSION

Utilizing the high resolution of OCT, several OCT studies have evaluated the *in-vivo* status of DES. The OCT-derived detection of an uncovered strut or neoatherosclerosis may be of use in preventing and predicting adverse cardiac events

such as the stent thrombosis. Moreover, advances in OCT technology are expected to reveal detailed changes in coronary stents and to widen the practical usefulness thereof.

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