Chapter 5

Visualization of Plaque Neovascularization by OCT

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1. Introduction

Although the introduction of drug-eluting-stents (DES) has dramatically reduced restenosis and the need for repeat revascularization compared with bare-metal stents (BMS), percutaneous coronary intervention (PCI) does not always prevent cardiac events, including acute coronary syndrome (ACS) [1]. Therefore, for all cardiologists, the detection of vulnerable plaques before they rupture is one of ultimate goals to predict and prevent ACS. Vulnerable plaques are characterized as thin fibrous cap (<65 μm), large lipid core, and macrophage infiltration within the cap. Furthermore, plaque neovascularization has been identified recently as a common feature of plaque vulnerability. Increased neovascularization in atherosclerotic plaques plays an important role in plaque progression, plaque instability, and rupture of plaque [2-5]. Until recently, however, in vivo studies assessing neovascularization in atherosclerotic plaques have been difficult because of the lack of sufficient resolution that reliably identifies this feature of vulnerable plaque. The first-generation catheter-based Time-domain optical coherence tomography (TD-OCT) system (M2 and M3 OCT system; LightLab Imaging, Westford, MA, USA), which offers superior resolution of 10-15 μm, has emerged as an intracoronary imaging modality, rendering the detailed micro-structure information of coronary plaques [6-8]. With its excellent resolution, OCT may provide an opportunity to directly detect plaque neovascularization in vivo. This chapter reviews the evidence of plaque neovascularization accumulated so far on OCT and discuss the future perspectives and limitations.

2. Neovascularization in atherosclerosis

Nourishment of normal blood vessels is accomplished by oxygen diffusion from the vessel lumen or from adventitial vasa vasorum [9]. As atherosclerosis progresses, the intima thickens, and oxygen diffusion is impaired. As a result, vasa vasorum proliferates in the inner

layers of the vessel wall, and becomes major source of nutrients. Vasa vasorum neovascularization in early atherosclerosis is associated with inflammatory cell infiltration and lipid deposition, leading to plaque progression [10]. Furthermore, intraplaque hemorrhage from microvessels contributes to expansion of the necrotic core through the accumulation of free cholesterol from erythrocyte membranes. Several human pathologic studies have demonstrated that plaque neovascularization is pronounced among patients with unstable coronary syndromes and that its presence may be a marker of plaque instability and plaque rupture [4, 5, 11]. Therefore, investigations of imaging methods with the ability to visualize neovascularization would appear worthwhile.

3. Potential imaging modalities of neovascularization

Several imaging modalities such as micro-computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound have emerged as potential techniques for imaging neovessels in atherosclerotic plaques. Micro-CT provides high-resolution images of coronary vasa vasorum neovascularization and insight into their structure and function in animal models [12, 13]. Winter et al have reported that molecular MRI with $\alpha v\beta 3$-targeted, paramagnetic nanoparticles can detect plaque neovessels in atherosclerotic rabbit model [14]. In addition, more recently, Sirol et al have demonstrated how gadofluorine M-enhanced MRI can accurately identify plaque neovascularization in an animal model of atherosclerosis with good histological correlation [15]. Thus, even though the results from these techniques are promising, further studies are needed for clinical application in humans. Intravascular ultrasound (IVUS) has the potential to detect flow within the plaque and subsequently evaluate functional neovessels. The development of IVUS-based imaging has recently demonstrated the preliminary data imaging neovascularization in coronary plaques in vivo after intravascular injection of microbubbles [16,17], but further investigations will be required to show the feasibility of this method for routine clinical use.

4. Plaque neovascularization by OCT

OCT has been proposed as a high-resolution imaging modality that can identify micro-structures in atherosclerotic plaques [8, 18, 19]. The superb high-resolution of OCT may offer an opportunity of studying the spatial distribution of plaque neovascularization in vivo (Figure 1) [20]. In fact, it has been shown that OCT is able to visualize neovascularization of atherosclerotic plaques [21-24]. In addition, Vorpahl et al demonstrated that small black holes in atheromatous plaques observed by OCT were in good agreement with the pathohistological evidence of intra-plaque neoangiogenesis formation in an autopsy case [25]. We recently assessed the relationship between intra-plaque microchannel structures identified by OCT, probably representing neovascularization, and plaque vulnerability in patients with coronary artery disease [21]. In this study, microchannel was defined as a no-signal tubuloluminal structure that was present on at least 3 consecutive OCT cross-sections in pull-back images. As a result, microchannels were seen in 38% of culprit plaques, and plaques with microchannels displayed the

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characteristics of vulnerability such as positive remodeling and thin fibrous caps compared with plaques without these structures. Of note, the presence of increased microchannel counts was correlated with a greater frequency of thin-capped fibroatheroma (TCFA) (Figure 2). More recently, in larger study population (356 plaques in 117 patients), Tian et al investigated the clinical significance of intra-plaque neovascularization in culprit lesions and no-culprit lesions of unstable angina pectoris (UAP) and in lesions of stable angina pectoris (SAP) using OCT [22]. Intra-plaque neovascularization was found in 35% of UAP culprit lesions, in 34% of UAP non-culprit lesions, and in 28% of SAP lesions, with no significant difference. Among UAP culprit lesions, plaques with neovessel had thinner fibrous cap thickness (56±20 μm vs. 75±30 μm, p<0.001) and significantly higher incidence of TCFA (81% vs. 47%, p=0.002) compared with those without neovessel. In addition, plaque burden was significantly bigger in UAP culprit lesions with neovascularization (79.8±7.9% vs. 72.8±10.7%, p=0.024). In terms of the non-culprit lesions of UAP patients and lesions of SAP patients, however, no significant difference in plaque characteristics was observed, regardless of the presence or absence of neovascularization. Interestingly, Kato et al reported that although the overall prevalence of microchannel in non-culprit lesions was not significantly different between ACS and non-ACS patients (64.7% versus 55.2%, respectively, P=0.647), the closest distance from the lumen to microchannel was shorter in ACS subjects than in non-ACS (104.6±67.0 μm versus 198.3±133.0 μm, p=0.027) [23]. The authors speculated that because neovascular networks expand from the adventitia into the intima as disease progresses [26], plaques with neovascularization located closer to the lumen might represent an advanced stage of atherosclerosis. Furthermore, Uemura et al revealed that microchannel structure in non-culprit plaques (defined as percent diameter stenosis of < 50%) identified by OCT is a predictor of subsequent plaque progression in patients with coronary artery disease [24].

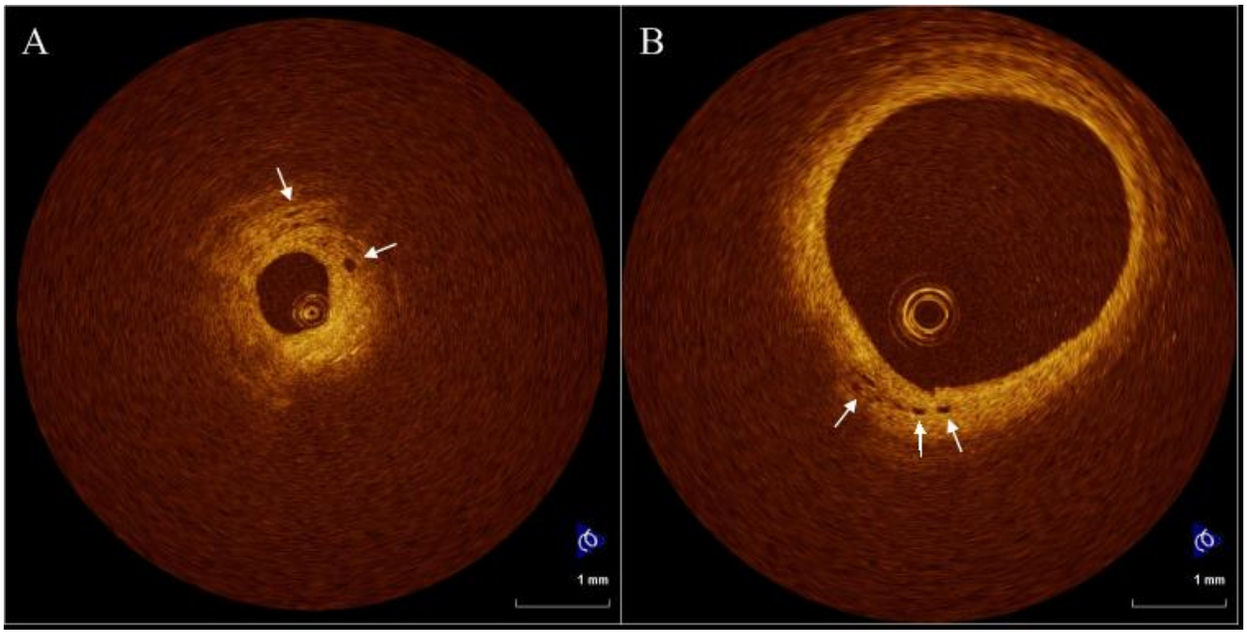

Figure 1. OCT (M2 system) images of plaque neovessels. Microvessels in the outer plaque (A) near the adventitia and (B) within the thickened intima can appear as signal-poor voids (white arrows) that are sharply delineated.

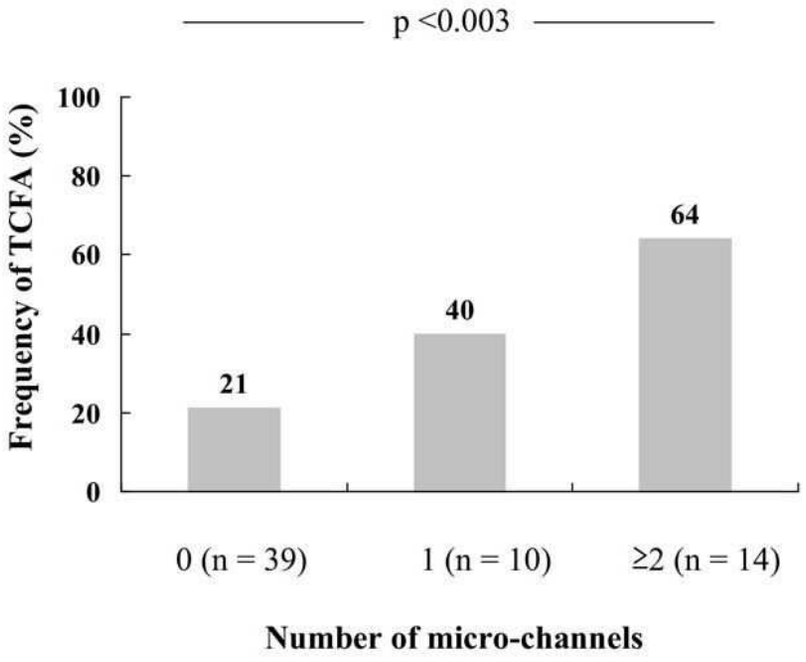

Figure 2. Comparison of frequency of TCFA according to number of microchannels. When categorized into 3 groups according to number of microchannels, the frequency of TCFA (21% in group with 0, 40% in group with 1, and 64% in group with ≥ 2; p < 0.003 for all) was significantly different. Reproduced with permission from [21].

5. Neovascularization inside the implanted stent by OCT

Although neovascularization within the neointima after stent implantation has been already reported in histopathologic studies [27, 28], Regar et al first reported in 2005 that OCT has an ability to visualize microvessels within the neointima inside the stents in a living human [29]. Later the presence of neovascularization in the stent restenosis was noted by Gonzalo et al [30]. However, the role of microvessels in restenotic tissue behavior has been unknown. More recently, Kim et al evaluated the characteristics of in-stent restenosis (ISR) lesions with microvessels detected by OCT [31]. Microvessels were detected in 21 (27%) of 78 ISR lesions. At the minimum lumen area site, the neointimal area (5.4 ± 1.7 mm^2 vs. 4.2 ± 2.1 mm^2, p=0.024) and percent neointimal area (79±12% vs. 67±16%, p=0.001) were significantly greater in ISR lesions with microvessels. These results suggest that microvessels within the neointima might be associated with restenosis by the excessive neointimal growth following stent implantation.

Furthermore, it has been shown that neointima in both BMS and DES can transform into atherosclerotic tissue with time although it occurs earlier in DES than BMS and that neoathrosclerosis progression inside the implanted stents may be associated with very late coronary events such as very late stent thrombosis after BMS and DES implantation [28, 32-40]. Using OCT, Takano et al examined the differences in neointima between early phase (< 6 months) and late phase (≥ 5 years) [35]. When compared with normal neointima proliferated

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homogeneously in the early phase, neointima inside the BMS ≥ 5 years after implantation was characterized by marked signal attenuation and a diffuse border, suggesting lipid-laden intima. Its frequency was 67% and lipid-laden intima was not observed in the early phase. TCFA-like intima was also found in 29% of the patients in the late phase. Intimal disruption and thrombus were observed more frequently in the late phase as compared with the early phase (38% vs. 0% and 52% vs. 5%, respectively; $p < 0.05$). Notably, although there was no significant difference in terms of the incidence of peristent neovascularization (Figure 3A) between the 2 phases (81% vs. 60%, p=0.14), intraintima neovascularization (Figure 3B) was seen more frequently in the late phase than in the early phase (62% vs. 0%, $p < 0.01$) and in segments with lipid-laden intima than those in without lipid-laden intima (79% vs. 29%, p=0.026). Moreover, Habara et al evaluated the difference of tissue characteristics between early (within the first year) and very late (> 5 years, without restenosis within the first years) restenostic lesions after BMS implantation by using OCT [39]. There was a significant difference in the morphological characteristics of restenostic tissue between very late ISR (characterized by heterogeneous intima) and early ISR (characterized by homogeneous intima). Intraintima microvessels were observed only in the very late ISR group (16.3% vs. 0%, p=0.01). Thus, expansion of neovascularization from persistent to intraintimal area with time may contribute to atherosclerosis progression of neointima, as well as intra-plaque neovascularization of nonstent segments in native coronary arteries.

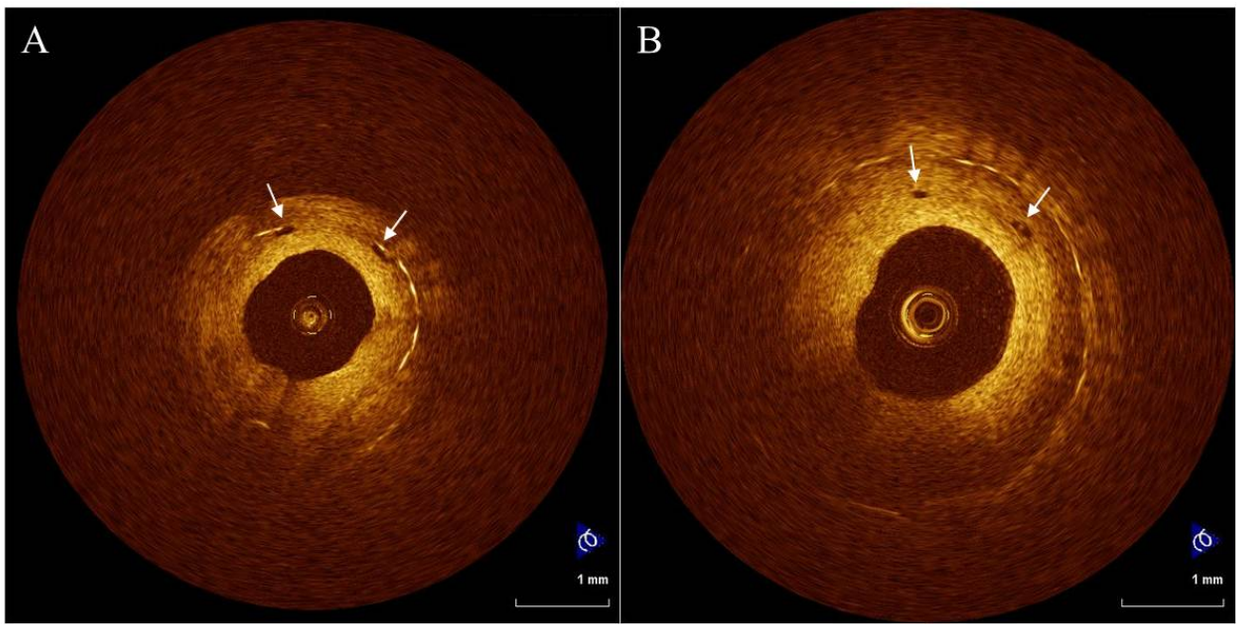

Figure 3. Neovascularization within neointima inside the implanted stent. (A) OCT (M2 system) image of peristent microvessels (arrows) demonstrating no-signal small vesicular and tubular structures locating around the struts. (B) OCT (M2 system) image of intraintima microvessels (arrows) showing small black holes locating near the vessel lumen within the neotintimal tissue.

6. Future perspectives (neovascularization as a therapeutic target for plaque stabilization)

For all cardiologists, stabilizing vulnerable plaques remains a major concern. Previous clinical trials have demonstrated that lipid-lowering therapy by statins stabilizes vulnerable plaques, thereby preventing cardiac events. Experimental studies have also shown that anti-atherosclerotic therapies can reduce plaque neovascularization [41-43] and that the inhibition of plaque neovascularization reduces progression of advanced atherosclerosis [41, 42]. Therefore, monitoring treatment effects of anti-atherosclerotic drugs using reliable surrogate markers may be useful to appropriately manage the patients. The thickness of fibrous cap in coronary plaque is a major determinant of plaque destabilization [44]. We recently reported that statins increased the fibrous cap thickness of plaques as assessed by OCT, indicating plaque stabilization [45, 46]. More recently, Tian et al investigated whether there was a difference in the effects of statin therapy between lesions with and without neovascularization [47]. As a result, despite a comparable reduction in serum cholesterol levels, the fibrous cap thickening was smaller in lesions with neovascularization than those without neovascularization after 6 and 12 months of statin treatment, which suggests that a more aggressive anti-atherosclerotic therapy may be required in patients with plaque with neovascularization. Thus, OCT allows us to monitor the response to anti-atherosclerotic therapies such as statins, and micro-channels in plaques identified by OCT could become a therapeutic target for plaque stabilization as important as the thickness of fibrous cap (Figure 4).

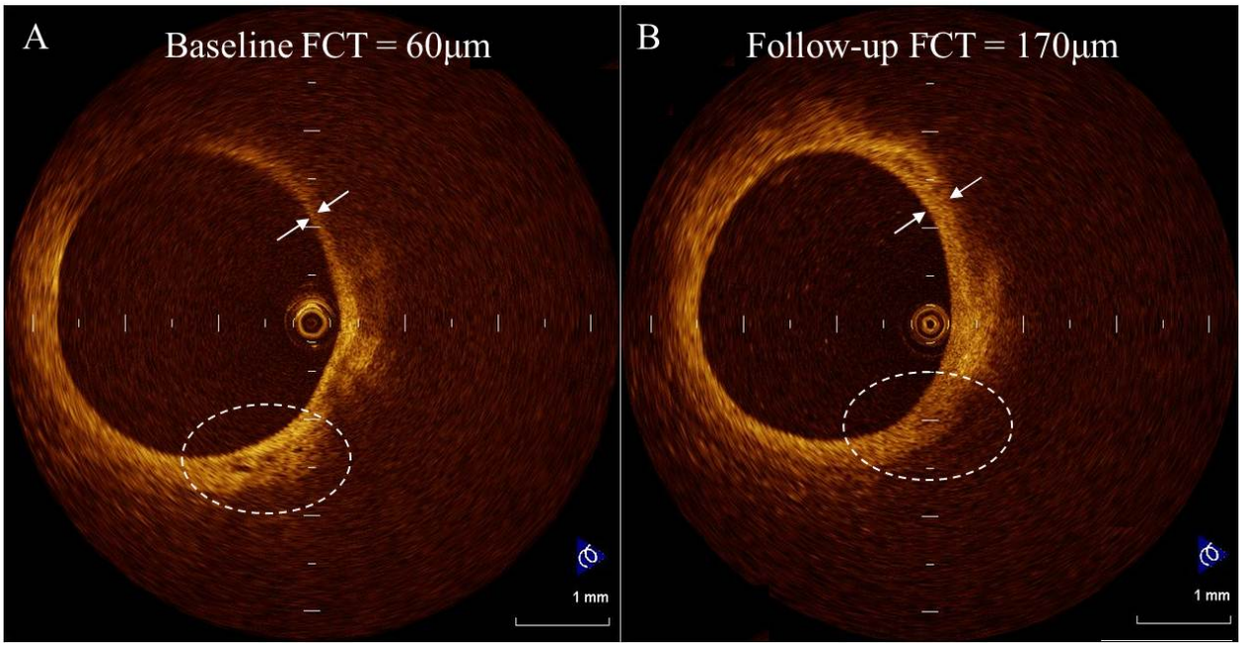

Figure 4. Plaque stabilization and elimination of neovascularization by statin treatment. (A) OCT (M2 system) demonstrates lipid-rich plaque covered by thin fibrous cap of 60 μm (thin-capped fibroatheroma) and microvessels at the shoulder region of the plaque (dotted circle). (B) Six months after statin treatment, the minimum fibrous cap thickness (FCT) increased from 60 μm to 170 μm and microvessels disappeared.

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Moreover, a newer-generation Frequency-domain OCT (FD-OCT; C7 system, LightLab Imaging) has recently been developed to overcome many of the technical limitations of TD-OCT system by imaging at much higher frame rates (100 frame/s), a larger scan diameter (10 mm) and a faster image acquisition rate (20 mm/s) without loss of image quality, and unlike TD-OCT, this technology does not require proximal balloon occlusion [48]. The imaging catheter of FD-OCT, which is designed for rapid exchange delivery, has a 2.7-Fr crossing profile and can be delivered over a 0.014-inch guidewire through a 6-Fr or larger guide catheter. Intracoronary injection of contrast media via the guide catheter (3 to 4 ml/s; 2-3 s) can achieve effective clearing of blood for the FD-OCT imaging. In combination with a short, nonocclusive flush and a faster pullback speed, the FD-OCT enables imaging of longer segments of coronary arteries without significant ischemia and motion artifact [49]. Thus, we would be able to more precisely and easily assess not only culprit but also nonculprit lesion morphologies in coronary artery disease by use of FD-OCT.

7. Limitations

First, because the penetration depth of OCT is relatively shallow (<2 mm), and OCT light signals are limited behind the lipid component or red thrombus, previous OCT studies may underestimate the presence of neovascularization. Second, neovessel size has been inconsistently defined by a wide range because it is unknown whether there is a threshold for the size of these vessels within the intima [50]. Finally, a direct comparison of OCT-derived microchannels with histology has not been done to date. Therefore, histological studies that properly validate these structures observed with in vivo OCT imaging are mandatory in the near future.

8. Conclusions

OCT has the potential to directly visualize neovascularization of atherosclerotic plaques in vivo. Microchannel structure in coronary plaques identified by OCT could be a marker of plaque vulnerability to improve patient risk stratification and a therapeutic target for plaque stabilization.

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References

[1] Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, Knudtson M, Dada M, Casperson P, Harris CL, Chaitman BR, Shaw L, Gosselin G, Nawaz S, Title LM, Gau G, Blaustein AS, Booth DC, Bates ER, Spertus JA, Berman DS, Mancini GB, Weintraub WS; COURAGE Trial Research Group. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med 2007;356(15):1503-1516.

[2] Jeziorska M, Woolley DE. Neovascularization in early atherosclerotic lesions of human carotid arteries: its potential contribution to plaque development. Hum Pathol 1999;30(8):919-925.

[3] Barger AC, Beeuwkes R, Lainey L, Silverman KJ. Hypothesis: vasa vasorum and neovascularization of human coronary arteries. N Engl J Med 1984;310(3):175-177.

[4] Barger AC, Beeuwkes R. Rupture of coronary vasa vasorum as a trigger of acute myocardial infarction. Am J Cardiol 1990;66(16):41G-43G.

[5] Tenaglia AN, Peters KG, Sketch MH Jr, Annex BH. Neovascularization in atherectomy specimens from patients with unstable angina: implications for pathogenesis of unstable angina. Am Heart J 1998;135(1):10-14.

[6] Kume T, Akasaka T, Kawamoto T, Watanabe N, Toyota E, Sukmawan R, Sadahira Y, Yoshida K. Assessment of coronary arterial plaque by optical coherence tomography. Am J Cardiol 2006;97(8):1172–1175.

[7] Kume T, Akasaka T, Kawamoto T, Watanabe N, Toyota E, Neishi Y, Sukmawan R, Sadahira Y, Yoshida K. Assessment of coronary intima-media thickness by optical coherence tomography: comparison with intravascular ultrasound. Circ J 2005;69(8): 903-907.

[8] Yabushita H, Bouma BE, Houser SL, Aretz HT, Jang IK, Schlendorf KH, Kauffman CR, Shishkov M, Kang DH, Halpern EF, Tearney GJ. Characterization of human atherosclerosis by optical coherence tomography. Circulation 2002;106(13):1640-1645.

[9] Moreno PR, Purushothaman KR, Sirol M, Levy AP, Fuster V. Neovascularization in human atherosclerosis. Circulation 2006;113(18):2245-2252.

[10] Virmani R, Kolodgie FD, Burke AP, Finn AV, Gold HK, Tulenko TN, Wrenn SP, Narula J. Atherosclerotic plaque progression and vulnerability to rupture: angiogenesis

as a source of intraplaque hemorrhage. Arterioscler Thromb Vasc Biol. 2005;25(10): 2054-2061.

[11] Moreno PR, Purushothaman KR, Fuster V, Echeverri D, Truszczynska H, Sharma SK, Badimon JJ, O'Connor WN. Plaque neovascularization is increased in ruptured atherosclerotic lesions of human aorta: implications for plaque vulnerability. Circulation 2004;110(14):2032-2038.

[12] Herrmann J, Lerman LO, Rodriguez-Porcel M, Holmes DR Jr, Richardson DM, Ritman EL, Lerman A. Coronary vasa vasorum neovascularization precedes epicardial endothelial dysfunction in experimental hypercholesterolemia. Cardiovasc Res 2001;51(4):762-766.

[13] Gössl M, Versari D, Mannheim D, Ritman EL, Lerman LO, Lerman A. Increased spatial vasa vasorum density in the proximal LAD in hypercholesterolemia; implications for vulnerable plaque-development. Atherosclerosis 2007;192(2):246-252.

[14] Winter PM, Morawski AM, Caruthers SD, Fuhrhop RW, Zhang H, Williams TA, Allen JS, Lacy EK, Robertson JD, Lanza GM, Wickline SA. Molecular imaging of angiogenesis in early-stage atherosclerosis with alpha (v) beta3-integrin-targeted nanoparticles. Circulation 2003;108(18):2270-2274.

[15] Sirol M, Moreno PR, Purushothaman KR, Vucic E, Amirbekian V, Weinmann HJ, Muntner P, Fuster V, Fayad ZA. Increased neovascularization in advanced lipid-rich atherosclerotic lesions detected by gadofluorine-M-enhanced MRI: implications for plaque vulnerability. Circ Cardiovasc Imaging. 2009;2(5):391-396.

[16] Vavuranakis M, Kakadiaris IA, O'Malley SM, Papaioannou TG, Sanidas EA, Naghavi M, Carlier S, Tousoulis D, Stefanadis C. A new method for assessment of plaque vulnerability based on vasa vasorum imaging, by using contrast-enhanced intravascular ultrasound and differential image analysis. Int J Cardiol 2008;130(1):23-29.

[17] Granada JF, Feinstein SB. Imaging of the vasa vasorum. Nat Clin Pract Cardiovasc Med 2008;5 Suppl 2:S18-25.

[18] Kubo T, Imanishi T, Takarada S, Kuroi A, Ueno S, Yamano T, Tanimoto T, Matsuo Y, Masho T, Kitabata H, Tsuda K, Tomobuchi Y, Akasaka T. Assessment of culprit lesion morphology in acute myocardial infarction: ability of optical coherence tomography compared with intravascular ultrasound and coronary angioscopy. J Am Coll Cardiol 2007;50(10):933-939.

[19] Jang IK, Tearney GJ, MacNeill B, Takano M, Moselewski F, Iftima N, Shishkov M, Houser S, Aretz HT, Halpern EF, Bouma BE. In vivo characterization of coronary atherosclerotic plaque by use of optical coherence tomography. Circulation 2005;111(12):1551-1555.

[20] Prati F, Regar E, Mintz GS, Arbustini E, Di Mario C, Jang IK, Akasaka T, Costa M, Guagliumi G, Grube E, Ozaki Y, Pinto F, Serruys PW; for the Expert's OCT Review Document. Expert review document on methodology, terminology, and clinical ap-

plications of optical coherence tomography: physical principles, methodology of image acquisition, and clinical application for assessment of coronary arteries and atherosclerosis. Eur Heart J 2009;31(4):401-415.

[21] Kitabata H, Tanaka A, Kubo T, Takarada S, Kashiwagi M, Tsujioka H, Ikejima H, Kuroi A, Kataiwa H, Ishibashi K, Komukai K, Tanimoto T, Ino Y, Hirata K, Nakamura N, Mizukoshi M, Imanishi T, Akasaka T. Relation of microchannel structure identified by optical coherence tomography to plaque vulnerability in patients with coronary artery disease. Am J Cardiol 2010;105(12):1673-1678.

[22] Tian J, Hou J, Xing L, Kim SJ, Yonetsu T, Kato K, Lee H, Zhang S, Yu B, Jang IK. Significance of intraplaque neovascularisation for vulnerability: optical coherence tomography study. Heart 2012 Aug 6. [Epub ahead of print]

[23] Kato K, Yonetsu T, Kim SJ, Xing L, Lee H, McNulty I, Yeh RW, Sakhuja R, Zhang S, Uemura S, Yu B, Mizuno K, Jang IK. Nonculprit plaques in patients with acute coronary syndromes have more vulnerable features compared with those with non-acute coronary syndromes: a 3-vessel optical coherence tomography study. Circ Cardiovasc Imaging 2012;5(4):433-440.

[24] Uemura S, Ishigami K, Soeda T, Okayama S, Sung JH, Nakagawa H, Somekawa S, Takeda Y, Kawata H, Horii M, Saito Y. Thin-cap fibroatheroma and microchannel findings in optical coherence tomography correlate with subsequent progression of coronary atheromatous plaques. Eur Heart J. 2012;33(1):78-85.

[25] Vorpahl M, Nakano M, Virmani R. Small black holes in optical frequency domain imaging matches intravascular neoangiogenesis formation in histology. Eur Heart J 2010;31(15):1889.

[26] Kumamoto M, Nakashima Y, Sueishi K. Intimal neovascularization in human coronary atherosclerosis: its origin and pathophysiological significance. Hum Pathol 1995;26(4):450-456.

[27] Komatsu R, Ueda M, Naruko T, Kojima A, Becker AE. Neointimal tissue response at sites of coronary stenting in humans: macroscopic, histological, and immunohistochemical analyses. Circulation 1998;98(3):224-233.

[28] Inoue K, Abe K, Ando K, Shirai S, Nishiyama K, Nakanishi M, Yamada T, Sakai K, Nakagawa Y, Hamasaki N, Kimura T, Nobuyoshi M, Miyamoto TA. Pathological analyses of long-term intracoronary Palmaz-Schatz stenting; Is its efficacy permanent? Cardiovasc Pathol 2004;13(2):109-115.

[29] Regar E, van Beusekom HMM, van der Gissen WJ, Serruys PW. Optical coherence tomography findings at 5-year follow-up after coronary stent implantation. Circulation 2005;112(23):e345–e346.

[30] Gonzalo N, Serruys PW, Okamura T, van Beusekom HM, Garcia-Garcia HM, van Soest G, van der Giessen W, Regar E. Optical coherence tomography patterns of stent restenosis. Am Heart J 2009;158(2):284-93.

[31] Kim BK, Kim JS, Shin DH, Ko YG, Choi D, Jang Y, Hong MK. Optical coherence tomography evaluation of in-stent restenotic lesions with visible microvessels. J Invasive Cardiol 2012;24(3):116-20.

[32] Hasegawa K, Tamai H, Kyo E, Kosuga K, Ikeguchi S, Hata T, Okada M, Fujita S, Tsuji T, Takeda S, Fukuhara R, Kikuta Y, Motohara S, Ono K, Takeuchi E. Histopathological findings of new in-stent lesions developed beyond five years. Catheter Cardiovasc Interv 2006;68(4):554-558.

[33] Yokoyama S, Takano M, Yamamoto M, Inami S, Sakai S, Okamatsu K, Okuni S, Seimiya K, Murakami D, Ohba T, Uemura R, Seino Y, Hata N, Mizuno K. Extended follow-up by serial angioscopic observation for bare-metal stents in native coronary arteries: from healing response to atherosclerotic transformation of neointimal. Circ Cardiovasc Intervent 2009;2(3):205-212.

[34] Kashiwagi M, Kitabata H, Tanaka A, Okochi K, Ishibashi K, Komukai K, Tanimoto T, Ino Y, Takarada S, Kubo T, Hirata K, Mizukoshi M, Imanishi T, Akasaka T. Very late cardiac event after BMS implantation: In vivo optical coherence tomography examination. J Am Coll Cardiol Img 2010;3(5):525-527.

[35] Takano M, Yamamoto M, Inami S, Murakami D, Ohba T, Seino Y, Mizuno K. Appearance of lipid-laden intima and neovascularization after implantation of bare-metal stents. J Am Coll Cardiol 2010;55(1):26-32.

[36] Hou J, Qi H, Zhang M, Ma L, Liu H, Han Z, Meng L, Yang S, Zhang S, Yu B, Jang IK. Development of lipid-rich plaque inside bare metal stent: possible mechanism of late stent thrombosis? An optical coherence tomography study. Heart 2010;96(15): 1187-90.

[37] Nakazawa G, Otsuka F, Nakano M, Vorpahl M, Yazdani SK, Ladich E, Kolodgie FD, Finn AV, Virmani R. The pathology of neoatherosclerosis in human coronary implants: bare-metal and drug-eluting stents. J Am Coll Cardiol 2011;57(11):1314-1322.

[38] Kang SJ, Mintz GS, Akasaka T, Park DW, Lee JY, Kim WJ, Lee SW, Kim YH, Whan Lee C, Park SW, Park SJ. Optical coherence tomographic analysis of in-stent neoatherosclerosis after drug-eluting stent implantation. Circulation 2011;123(25): 2954-2963.

[39] Habara M, Terashima M, Nasu K, Kaneda H, Inoue K, Ito T, Kamikawa S, Kurita T, Tanaka N, Kimura M, Kinoshita Y, Tsuchikane E, Matsuo H, Ueno K, Katoh O, Suzuki T. Difference of tissue characteristics between early and very late restenosis lesions after bare-metal stent implantation: an optical coherence tomography study. Circ Cardiovasc Interv 2011;4(3):232-238

[40] Kitabata H, Kubo T, Komukai K, Ishibashi K, Tanimoto T, Ino Y, Takarada S, Ozaki Y, Kashiwagi M, Orii M, Shiono M, Shimamura K, Hirata K, Tanaka A, Kimura K, Mizukoshi M, Imanishi T, Akasaka T. Effect of strut thickness on neointimal atherosclerotic change over an extended follow-up period (≥ 4 years) after bare-metal stent

implantation: intracoronary optical coherence tomography examination. Am Heart J 2012;163(4):608-616.

[41] Moulton KS, Heller E, Konerding MA, Flynn E, Palinski W, Folkman J. Angiogenesis inhibitors endostatin or TNP-470 reduce intimal neovascularization and plaque growth in apolipoprotein E-deficient mice. Circulation 1999;99(13):1726-1732.

[42] Moulton KS, Vakili K, Zurakowski D, Soliman M, Butterfield C, Sylvin E, Lo KM, Gillies S, Javaherian K, Folkman J. Inhibition of plaque neovascularization reduces macrophage accumulation and progression of advanced atherosclerosis. Proc Natl Acad Sci U S A 2003;100(8):4736-4741.

[43] Wilson SH, Herrmann J, Lerman LO, Holmes DR, Napoli C, Ritman EL, Lerman A. Simvastatin preserves the structure of coronary adventitial vasa vasorum in experimental hypercholesterolemia independent of lipid lowering. Circulation 2002;105(4): 415-418.

[44] Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. Arterioscler Thromb Vasc Bio 2000;20(5):1262-1275.

[45] Takarada S, Imanishi T, Kubo T, Tanimoto T, Kitabata H, Nakamura N, Tanaka A, Mizukoshi M, Akasaka T. Effect of statin therapy on coronary fibrous-cap thickness in patients with acute coronary syndrome: Assessment by optical coherence tomography study. Atherosclerosis 2009;202(2):491-497.

[46] Takarada S, Imanishi T, Ishibashi K, Tanimoto T, Komukai K, Ino Y, Kitabata H, Kubo T, Tanaka A, Kimura K, Mizukoshi M, Akasaka T. The effect of lipid and inflammatory profiles on the morphological changes of lipid-rich plaques in patients with non-ST-segment elevated acute coronary syndrome: follow-up study by optical coherence tomography and intravascular ultrasound. J Am Coll Cardiol Intv 2010;3(7): 766-772.

[47] Tian J, Hou J, Xing L, Kim SJ, Yonetsu T, Kato K, Lee H, Zhang S, Yu B, Jang IK. Does neovascularization predict response to statin therapy? Optical coherence tomography study. Int J Cardiol 2012;158(3):469-470.

[48] Barlis P, Schmitt JM: Current and future developments in intracoronary optical coherence tomography imaging. EuroIntervention 2009;4(4):529-533.

[49] Takarada S, Imanishi T, Liu Y, Ikejima H, Tsujioka H, Kuroi A, Ishibashi K, Komukai K, Tanimoto T, Ino Y, Kitabata H, Kubo T, Nakamura N, Hirata K, Tanaka A, Mizukoshi M, Akasaka T. Advantage of next-generation frequency domain optical coherence tomography compared with conventional time-domain system in the assessment of coronary lesion. Catheter Cardiovasc Interv 2010;75(2):202-206.

[50] Tearney GJ, Regar E, Akasaka T, Adriaenssens T, Barlis P, Bezerra HG, Bouma B, Bruining N, Cho JM, Chowdhary S, Costa MA, de Silva R, Dijkstra J, Di Mario C, Dudek D, Falk E, Feldman MD, Fitzgerald P, Garcia-Garcia HM, Gonzalo N, Granada

JF, Guagliumi G, Holm NR, Honda Y, Ikeno F, Kawasaki M, Kochman J, Koltowski L, Kubo T, Kume T, Kyono H, Lam CC, Lamouche G, Lee DP, Leon MB, Maehara A, Manfrini O, Mintz GS, Mizuno K, Morel MA, Nadkarni S, Okura H, Otake H, Pietrasik A, Prati F, Räber L, Radu MD, Rieber J, Riga M, Rollins A, Rosenberg M, Sirbu V, Serruys PW, Shimada K, Shinke T, Shite J, Siegel E, Sonoda S, Suter M, Takarada S, Tanaka A, Terashima M, Thim T, Uemura S, Ughi GJ, van Beusekom HM, van der Steen AF, van Es GA, van Soest G, Virmani R, Waxman S, Weissman NJ, Weisz G; International Working Group for Intravascular Optical Coherence Tomography (IWG-IVOCT).Consensus standards for acquisition, measurement, and reporting of intravascular optical coherence tomography studies: a report from the International Working Group for Intravascular Optical Coherence Tomography Standardization and Validation. J Am Coll Cardiol 2012;59(12):1058-1072.

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