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REVIEW ARTICLE

Coronary angioscopy: current topics and future direction

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Abstract Disruption of vulnerable plaque and following thrombus formation are considered the main cause of acute coronary syndrome (ACS). Intracoronary angioscopy is an endoscopic technology that allows direct visualization of the coronary artery lumen and provides detailed information regarding plaque morphology in patients with coronary artery disease. The color and morphology of coronary plaque under angioscopy observation are proposed to be determinants for plaque stability. Angioscopically yellow plaque represents a thin-cap fibroatheroma, and is associated with a higher incidence of disruption and thrombus formation, and may be associated with future acute coronary syndromes. To circumvent the subjectivity of color interpretation, various quantitative methods have been proposed for identifying vulnerable plaques. Superior to other coronary imaging techniques such as VH IVUS and optical coherence tomography, angioscopy has impressively high sensitivity and specificity in detection of intraluminal thrombus. Angioscopy can also be used as an adjunctive technique during catheter intervention by directly visualizing the thrombus, stent struts and proliferating neointima. The time course and pattern of neointima coverage, as seen by angioscopy, various among different stent systems. Angioscopic assessment of serial changes after stent implantation may have potential benefits on patient's management after coronary stenting.

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Keywords Angioscopy · Stent · Thrombus · Vulnerable plaque

Introduction

Angiography has been used for many years as the "gold standard" to evaluate coronary atherosclerotic lesions and results of interventional therapy. However, angiography can only provide a two-dimensional silhouette of the lumen and cannot thoroughly display the complex nature of endothelial dysfunction, vulnerable plaque disruption and thrombosis formation leading to dissociation between the angiogram and clinical outcomes [1]. It has been recognized that almost two-thirds of acute coronary events occur in angiographically noncritical lesions [2]. Identification of vulnerable plaques and arterial wall pathology are, therefore, essential, to enable the development of treatment modalities for coronary artery diseases. Various invasive and non-invasive diagnostic tools aimed at these purposes include angioscopy, intravascular ultrasound, spectroscopy, thermography, optical coherence tomography, computed tomographyand magnetic resonance imaging. Among these modalities, coronary angioscopy allows direct visualization of the internal surface of a vessel, providing the detailed information regarding characteristics of the plaque and thrombus. This technique provides insight into the underlying pathophysiology of acute coronary syndrome and information regarding the pathologic changes after coronary intervention. In Japan, angioscopy is an officially approved diagnostic method during angioplasty, and is now supported by the national health insurance. In the current review article, update on the technique and clinical application of coronary angioscopy are discussed.

Performance of angioscopy

Modern angioscopy started back in 1913 by Rhea and Walker with attempts to evaluate cardiac disorders endoscopically. With the marked improvements in this technique, especially in the decreased diameter of the optical equipment and increased fiber count, in 1983, percutaneous coronary angioscopy was first performed during cardiac catheterization using the Olympus fiberscope® which allowed visualization of right coronary artery [3]. In 1989, the over-the-guidewire type of angioscopy was developed. In this system, a specially made balloon, fixed at the distal tip, was mounted on the angioscopic catheter [4]. Another important improvement occurred in 1991 with the development of the coronary "Image Cath®" system (Baxter Healthcare Corporation, USA).

Modern angioscopic imaging system is made up of xenon lamplight source, imaging fibers, charge-coupled-device (CCD), color camera, monitor and a videotape recorder. An angioscope catheter is usually composed of a fiber-optic bundle of 3000 pixels, and is guided within the coronary artery over a conventional 0.014-inch angioplasty guidewire.

A principal advantage of angioscopy is that it allows visualization of the surface morphology characteristics of the coronary arterial wall in living patients with high resolutions (10–50 μm). Intracoronary angioscopy can also offer a direct visualization of the intra-luminal structures like thrombus with the sensitivity higher than angiography [5]. Studies indicated that yellow plaques under angioscopic observation seem to have an increased instability and acute coronary syndromes occur more frequently in patients with yellow plaques [6, 7]. These features have been responsible for a considerable expansion of coronary angioscopy in clinical settings. Figure 1 shows the classification of coronary surface changes observed by angioscopy.

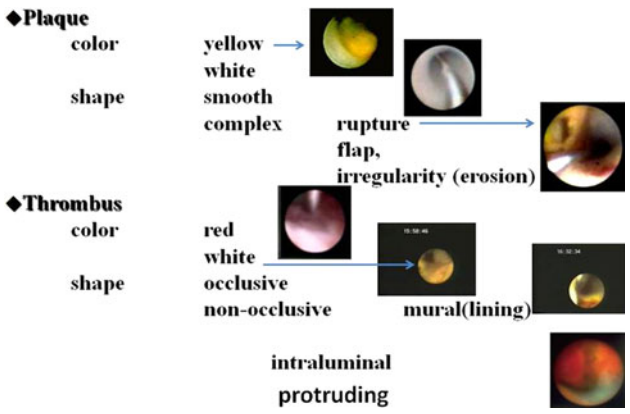

Fig. 1 Classification of coronary angioscopic finding. Plaque is classified in yellow and white according to the color, smooth or complex according to the shape. Thrombus is classified into red and white according to the color, and mural or transluminal according to their shapes

Comparison between angioscopy and pathology

Angioscopy enables us a direct visualization and accordingly macroscopic pathological evaluation of plaque surface and intra-luminal structures like tears and thrombi. It allows pathological diagnosis of coronary artery disease from inside. With its three-dimensional imaging ability and capability of color discrimination, the angioscopic findings had a high degree of agreement with histologic observations in characterizing normal artery, stable plaque, disrupted plaque, and thrombus.

Atherosclerotic plaque

Atherosclerosis is a progressive and chronic disease that affects the arterial vessel wall. Changes of the luminal surface and patency may ultimately lead to dire consequences. Some of these changes can be explored with angioscopy and contribute to the understanding of the mechanisms underlying acute coronary syndromes. (Fig. 2).

The normal artery appears angioscopically smooth in contour, without any protruding structure, and has a uniform glistening white. Whereas atherosclerotic plaque (atheroma) can be categorized on the basis of its angioscopic characteristics as yellow or white, lining or protruding and continuous with the normal vessel wall. Although coronary angioscopy has provided a unique insight into coronary artery disease, the inherent qualitative nature of angioscopic data has limited its application. Chromatic distortions and the subjectivity of human color perception substantially limit the theoretical potential of angioscopic color. Methods of image quantification, such as quantitative colorimetric analysis, has been developed to overcome the limitations inherent in angioscopic data and provide objective, reproducible analysis of angioscopic images [8–10]. In addition, the latest in vitro studies indicate that by using color fluorescent angioscopy (CFA), the yellow coronary plaques observed by conventional angioscopy can be further classified into green, white-to-light blue, and yellow-to-orange plaque according to their component, such as collagen subtypes, oxidized LDL, macrophage foam cells and calcium, thus provide much more objective information to identify vulnerable plaque [11].

Vulnerable plaque

"Vulnerable plaque" refers to a subgroup of plaques that are prone to rupture [12].

Numerous reviewers have described that vulnerable plaques have a thin, fibrous cap; a large, lipid-rich pool; and increased inflammatory activity [13, 14]. Rupture of

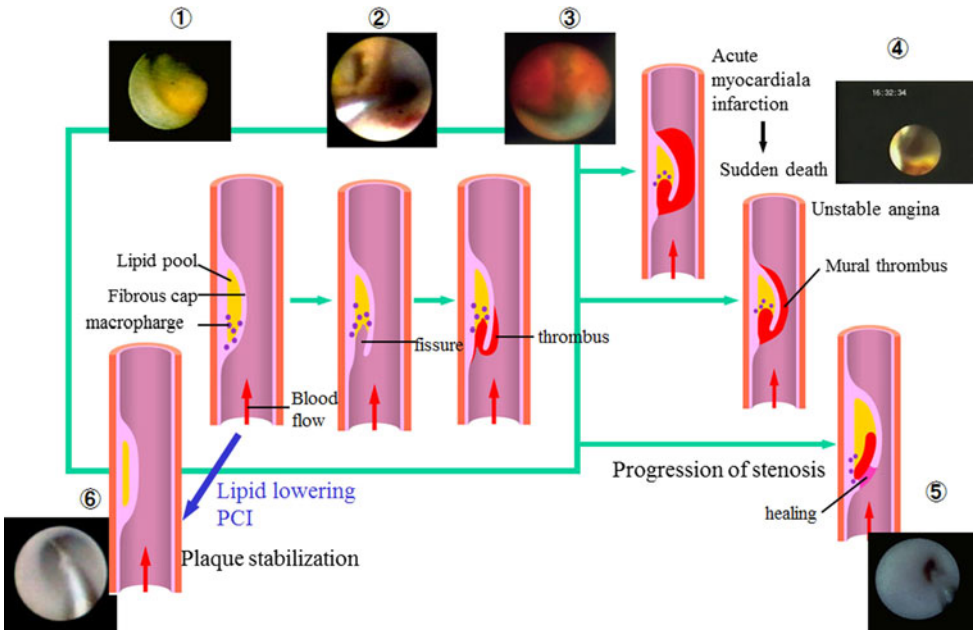

Fig. 2 Thrombus formation (③ ④) secondary to the rupture of vulnerable plaque (yellow plaque ① ②) plays a major role in acute coronary syndrome. Healing of vulnerable plaque or organization of thrombus (⑤) increases stenotic severity

vulnerable plaques is the main cause of acute coronary syndrome. Identification of vulnerable plaque is, therefore, essential to enable the development of diagnosis, treatment, and prevention of ischemic coronary disease. Among all the invasive diagnostic modalities, angioscopy is the only method that can observe the luminal surface of plaque by detecting the yellow color intensity of plaque. Histopathologic analysis of specimens of coronary lesions from patients receiving directional coronary atherectomy treatment demonstrate high concentrations of lipid component seen through a thin, fibrous cap in angioscopically yellow plaque [15]. A comparative autopsy study also suggests that yellow plaque had a thinner fibrous cap (58 ± 18 μm vs. 648 ± 356 μm $p < 0.0001$) and a lager lipid core compared to the white plaque [16]. By injecting lipid into bovine aorta at different depths, in vitro histologic studies further demonstrate the intensity of yellow color, as observed with angioscopy, inversely correlated with the fibrous cap thickness [17]. Yellow plaques with a higher color grade also have a higher prevalence of adherent thrombus [18] and positive remodeling [7]. Acute coronary syndromes occurred more frequently in patients with yellow plaque than in those with white plaques [19]. However, yellow plaque has also been demonstrated in patients of asymptomatic stable angina by angioscopy [20]. The glistening yellow plaques seen during angioscopy are associated with higher prevalence of future acute coronary syndromes comparing with non-glistening yellow plaques [6] and the number of yellow plaque was also associated with higher prevalence of cardiovascular events [21]. In AMI, patients who have had percutaneous coronary intervention, angioscopic thick yellow plaque is associated with long-term favorable prognosis [22].

Plaque erosion without lipid core rupture can also be detected under angioscopy examination. Smaller infarct size were demonstrated in the plaque erosion group than in the plaque rupture group of patients with acute myocardial infarction [23]. Moreover, slow-flow phenomenon, abrupt closure after POBA and embolic substances collected by distal protection device are more often observed in patients with ruptured plaque lesions than those with eroded plaque [24].

Thrombus

Angioscopic thrombi are defined as a red, white or mixed red and white mass, adhering to the intima and/or protruding into the lumen. An angioscopic study including 31 patients has reported the significantly higher prevalence of reddish thrombi in patients with acute myocardial infarction, on the other hand grayish-white thrombi were observed in patients with unstable angina and NSTEMI [25]. The color differences observed by angioscopy may reflect the variations in thrombus composition. At the early stage of the formation, the thrombus is platelet rich and appearing with a white cotton-like surface under angioscopic observation [26]. With lapse of time, the thrombus color changes to red angioscopically because of the abundance of fibrin mixed with erythrocytes. Finally, the color of the thrombus shifts progressively toward a smooth, white color as organization progresses (Fig. 2). The color differences of thrombus may be observed via angioscopy among patients with varying acute coronary syndromes. This pathological presentation may explain why the thrombolysis treatment using tPA is less effective in patients with unstable angina or NSTEMI27.

Angioscopy versus VH IVUS and OCT

VH IVUS uses advanced spectral analysis of ultrasound signals to provide a more detailed analysis of plaque composition. Thin cap fibroatheroma (TCFA) is considered to be vulnerable plaque and is frequently found in patients who died from ACS. Both modalities, IVUS-VH and angioscopy, can be used complementarily in TCFA evaluation. In a comparative study betweenVH IVUS and angioscopy, when angioscopic-TCFA intense yellow plaque was used as the gold standard, the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy for VH-TCFA was 68, 81, 74, 76, and 75%, respectively [27]. The amount of necrotic core detected by VH IVUS also correlates with the plaque color detected by angioscopy. Mean percentage of necrotic core analyzed by VH IVUS is significantly larger in angioscopically yellow plaque than in white plaque [28]. However VHIVUS has limitations in assessment of intramural thrombus. The current classification tree for VH IVUS analysis cannot differentiate the presence of intramural thrombus due to difficulties in differentiating the borderline between intramural thrombus and fibrous plaque. By using histologic findings as reference, angioscopy had an excellent sensitivity for thrombus (100%) [29], whereas VH IVUS falsely identify the intramural thrombus as fibrous or fibrofatty [30].

With its extremely high spatial resolution, optical coherence tomography (OCT) provides accurate tissue characterization in vivo and has the capability to characterize the component of plaque with the sensitivity and specificity of 92 and 94% respectively [31]. In comparative studies, angioscopic color intensity is correlated with the fibrous cap thickness estimated by optical coherence tomography. Yellow plaques of higher color grade might have a thinner fibrous cap, and 80% of intensive yellow plaque was TCFA [32, 33]. Figure 3 shows the inverse relationship between color grade by angioscopy and the fibrous cap thickness by OCT. In a study of postmortem human arterial segments, the sensitivity of angioscopy was 74% for plaque rupture detection (specificity and positive predictive value were over 90%) and 100% for thrombus detection, revealing that angioscopy may have underestimated the presence of plaque rupture [28]. Previous investigation of patients with acute coronary syndrome demonstrated that in comparison with angioscopy, OCT showed a similar frequency for the detection of thrombus and a higher frequency for the detection of plaque rupture [34]. Current limitation of OCT as well as angioscopy is the need to displace blood in the imaging zone. But with the introduction of new technology, the next generation of OCT will reach faster pullback speeds and no need the use of balloon occlusion.

In comparison with IVUS-VH and OCT, angioscopy has the superior ability to provide full color, real time, three dimensional, and direct visualization of coronary lumen and plaque surface. In particular, vulnerable plaque can be identified as yellow plaque under angioscopy feasibly and simpler than the complex imaging acquisition procedures of IVUS-VH and OCT. Furthermore, angioscopy may be the most powerful technique to detect thrombus formation than any other coronary imaging modalities.

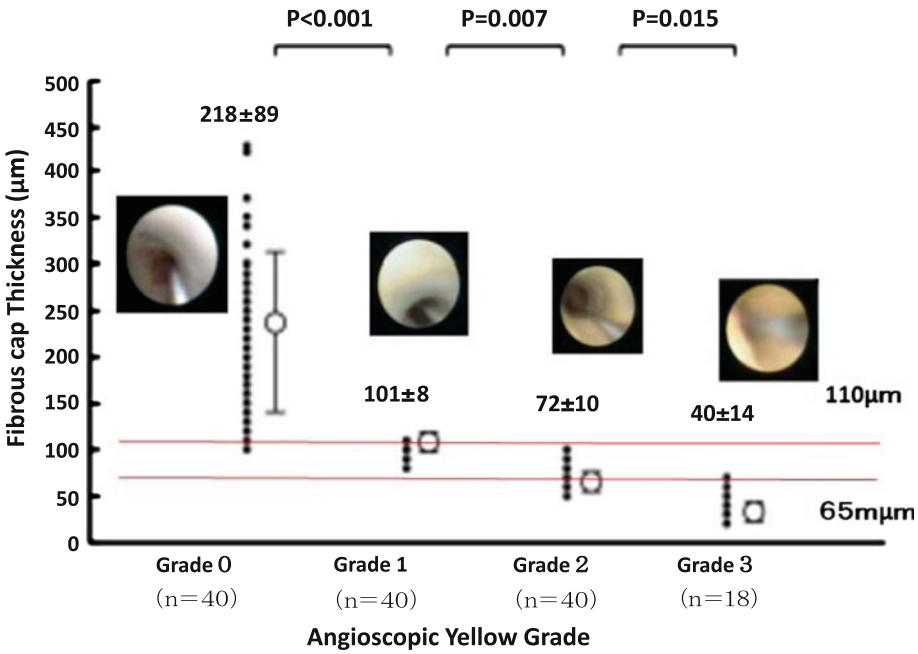

Fig. 3 Relationship between the angioscopic yellow grade and the fibrous cap thickness measured by optical coherence tomography (*OCT*). The fibrous cap thickness by OCT decreased significantly as yellow grade by angioscopy rose

Angioscopic findings after stent implantation

Stent implantation (conventional bare metal stents BMS and current DES) has been widely used for effective treatment of obstructive coronary artery disease and was shown to significantly improve the outcome compared to angioplasty alone. However, restenosis and in stent thrombosis are still the main limitation of coronary stenting. Although contrast angiography remains the clinical standard for coronary imaging, it is deficient in quantifying minimal changes of the artery wall after stent implantation. Angioscopy is superior to angiography in detecting thrombus. In one study, 15 patients were examined by coronary angioscopy during stent placement, intravascular thrombus, undetected by angiography, was found in two cases, while four patients had residual narrowing requiring redilation [35].

BMS

Early stent thrombosis has been reported in ACS patients with bare-metal stents at one-month follow up and disappeared within 6 months [36, 37]. Angioscopy has been used to evaluate the time course of neointimal coverage of stents. According to the pathological study, approximately 3 months were required for the completion of neointimal stent coverage after BMS implantation. The neointimal coverage after BMS implantation was angioscopically classified into 5 grades [38] as shown in Fig. 4. Immediately and approximately 2 weeks after BMS implantation, no neointimal coverage was found angioscopically in any cases [39, 40]. Complete stent endothelialization, observed angioscopically as smooth white neointima covering the stent struts, was found at 65–142 days and 6 months after stenting. Plaque morphology on angioscopy may affect the artery healing process after BMS implantation. A serial angioscopic study of patients with AMI has demonstrated that at 1 months' follow-up the grade of neointimal stent coverage is lower in the ruptured segment of infarct-related lesions than in the adjacent nonruptured segment [40]. Transparency of neointima under angioscopy, which was associated with the thickness of the neointima, gradually decreased from 3 to 6 months after BMS stenting. However, long-term follow up with angioscopy revealed that thick non transparent neointima shifts into thin and transparent appearance 3 years after stenting [41]. This regression process may be associated with decrease of cellular components and apoptosis [42]. Furthermore, atherosclerotic transformation inside the BMS segment has been reported in an extended long term follow-up study utilizing both angioscopy and OCT [43]. Inside the stent segment, vulnerable atherosclerotic plaque with thrombus protruding from the vessel wall into the lumen was identified angioscopically beyond 4 years after BMS implantation (Fig. 5). This phenomenon may contribute to late luminal narrowing after BMS implantation.

DES

Drug eluting stents (DES) have demonstrated a major breakthrough in the reduction of neointimal hyperplasia and thereby reducing restenosis compared with BMS. However, delayed neointimal coverage with drug-eluting stents may prolong the period of high risk for stent thrombosis. This was illustrated in a comparative angioscopic study between the first generation DES, sirolimus-eluting stents (SES) and BMS [44]. At 3–6 months after stent implantation, 3 of the 15 SES (20%) had essentially no neointimal coverage, and only 2 SES (13.3%) had complete coverage. In contrast, all 22 BMS showed complete intimal coverage. Thrombi were more common in stents with incomplete neointimal coverage. Serial angioscopic findings revealed that subclinical thrombus formation associated with delayed neointimal coverage over struts persists for up to 2 years after SES implantation [45] and we have experienced a case of acute myocardial infarction caused by late stent thrombosis 31 months after SES implantation (Fig. 6) [46]. Another study compared

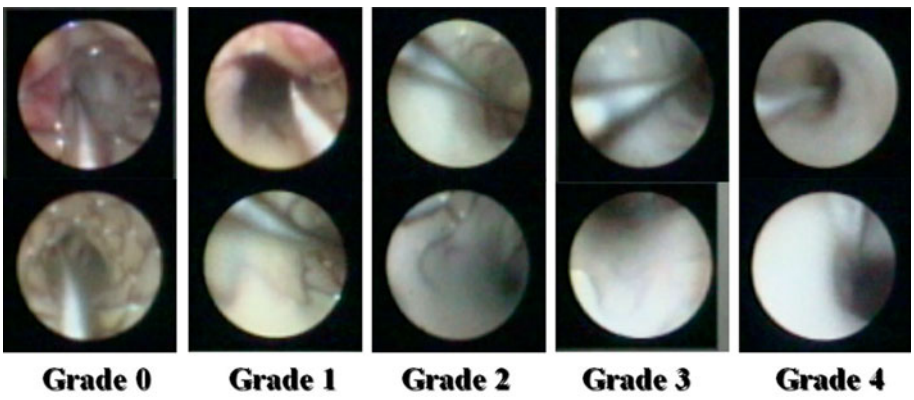

Fig. 4 Stent coverage score evaluated by coronary angioscopy. *Grade 0* complete exposure of stentstruts. *Grade 1* exposure of stent struts with partial coverage. *Grade 2* >50% coverage of stent. *Grade 3* almost complete coverage with slightly visible stent struts. *Grade 4* complete coverage of stent struts

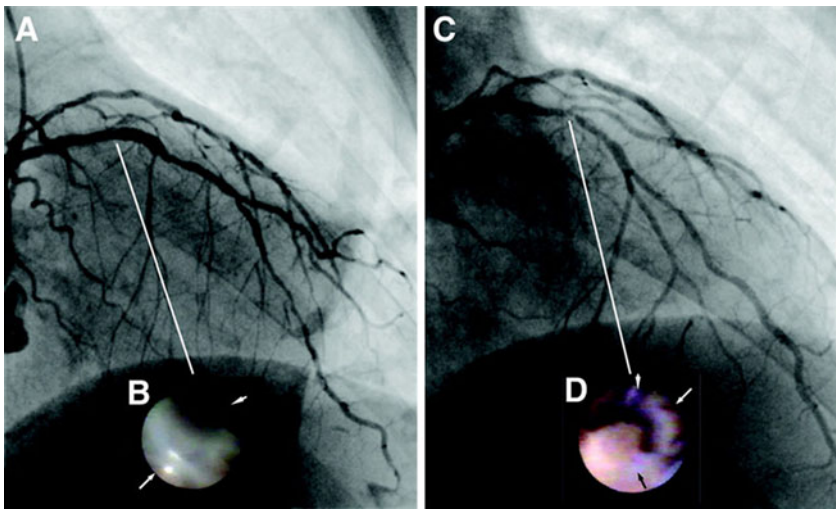

Fig. 5 Angiographic and angioscopic findings of the second follow-up. *A* Second follow-up examinations were performed 10 years after GFX® stent implantation in the left anterior descending artery. The percent diameter stenosis at the second follow-up is 11.7%. *B* An angioscopy shows the presence of the white intima. The neointima is partially transparent and a part of the stent struts is visible (*white arrow*). *C* In another case, the second follow-up was performed 9 years after Multilink® stent implantation in the left anterior descending artery. Although restenosis was not observed at the first follow-up (7 months), new in-stent restenosis was found at the second follow-up. Late luminal narrowing is 43.8%. *D* In the segment corresponding to the in-stent restenosis, protruding yellow plaque is identified by angioscopy. There are visible struts (*white arrow*) distal to the yellow plaque. A *white arrowhead* indicates a guide wire

SES with the next generation DES, zotarolimus eluting stent (ZES). In this study ZES showed greater neointimal coverage grades than SES [47] 8 months after implantation, 71% of ZES showed grade 3 neointimal coverage, whereas only 6% of sirolimus-eluting stents (SES) showed grade 3 coverage. However, because of the high incidence of late loss of ZES compared to the SES, ZES may lead to the higher restenosis rate in the treatment of small vessels and complex lesion. On the other hand, another first generation DES paclitaxel-eluting stent (PES) showed intermediate late loss among these DESs. To investigate whether PES has the better effect on the endothelial healing process, angioscopy was performed 9 ± 2 months after 30 PES and 36 SES implantation [48]. In contrast to the 53% homogenous neointimal coverage of SES, PES showed heterogeneous neointimal coverage (48% showed the heterogeneity of grade 1; 26% showed the heterogeneity of grade 2) associated with a higher incidence of thrombi. Even at 18 months after stent implantation, PES still shows more heterogeneous neointimal coverage and higher incidence of thrombus formation as compared with SES [49]. This angioscopic finding indicates that homogeneous neointimal coverage may be an important factor for competent arterial healing after DES deployment.

Several studies have also demonstrated a significant association of delayed neointimal coverage with underlying yellow plaque that is generally sealed by white smooth neointima by 1 year in BMS but often continues to be exposed in DES [50, 51]. Comparing with the baseline, the maximum yellow color grade of the neointima within DES-implanted lesions increased significantly at 10 months' follow-up after stenting. Yellow color was even newly developed in 94% of lesions with no yellow plaque at baseline [51]. Vascular response to DES, including inflammatory and endothelial dysfunction, might contribute to the atherosclerotic process that differ from BMS.

It should be noted that angioscopy may underestimate endothelialization because of the limited image resolution. Data from in vitro experimental porcine coronary model show that stents, which looked uncovered as seen by macroscopy, appeared completely covered by endothelium as assessed by scanning electron microscopy [52].

Limitations and new techniques of angioscopy

Although coronary angioscopy has provided unique insight into coronary artery disease, the inherent qualitative nature of angioscopic data has limited its application. Chromatic distortions and the subjectivity of human color perception substantially limit the theoretical potential of angioscopic color. Methods of image quantification, such as quantitative colorimetric analysis, has been developed to overcome the limitations inherent in angioscopic data and provide objective, reproducible analysis of angioscopic images [8–10]. In addition, the latest in vitro study indicates that by using color fluorescent angioscopy (CFA), the yellow coronary plaques observed by conventional angioscopy can

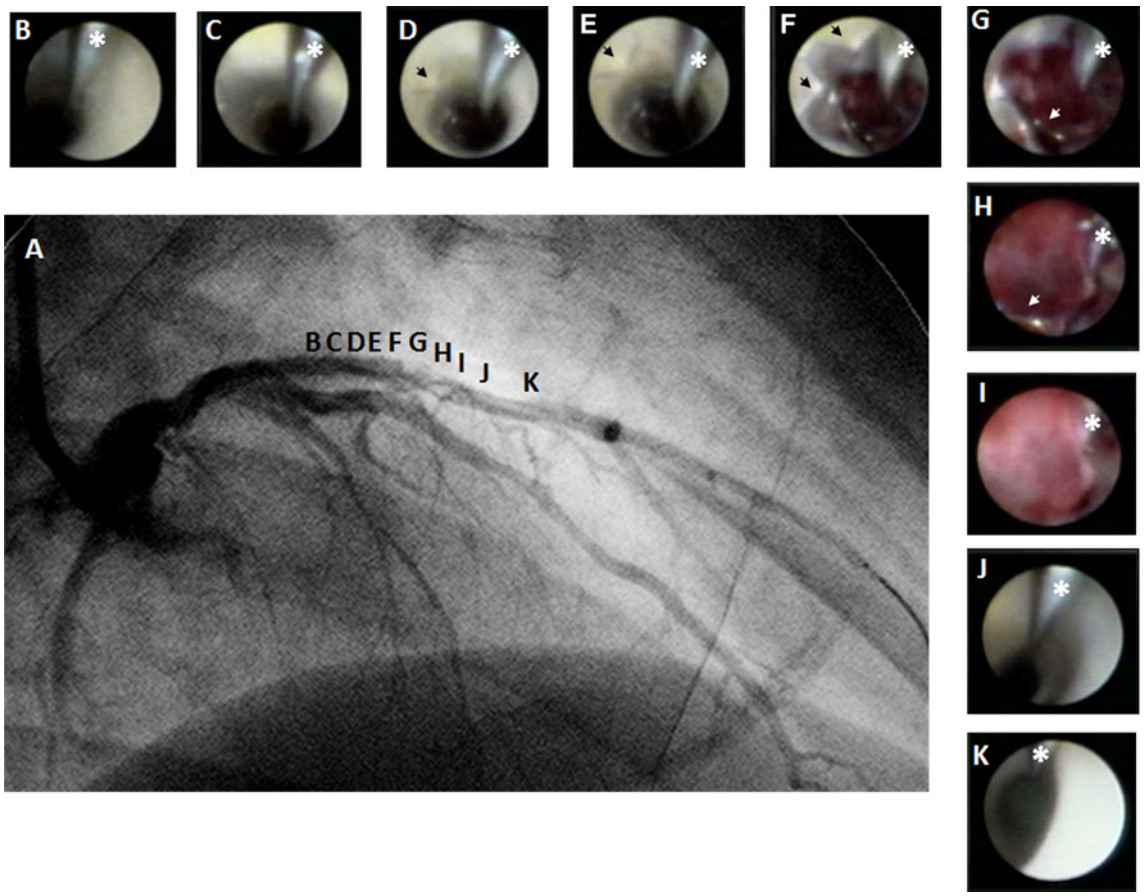

Fig. 6 A case of late thrombosis after stenting with drug eluting stent (DES) At 31 months after sirolimus-eluting stent (*SES*) implantation, massive and protruding red thrombi adjacent to exposed stent and a lack of macroscopic neointimal coverage (*white arrow*) are observed in the large proximal diagonal branch. An *asterisk* indicates guide wire

be further classified into green, white-to-light blue, and yellow-to-orange plaque according to their component, such as collagen subtypes, oxidized LDL, macrophage foam cells and calcium,thus provide much more objective information to identify vulnerable plaque [11].

Conclusion

Angioscopy can provide a full-color, 3-dimensional perspective of the intracoronary surface morphology that heretofore has been available only at necropsy. These important lesion-specific details can be used to detect vulnerable plaques and enhanced our understanding of the mechanisms of percutaneous interventions. Despite the limitations such as the need of balloon occlusion, angioscopy is currently performed with high success and low complication rates in Japan. In the future, with improvements in technology and perspective large-scale studies, angioscopy will not only be potentially valuable for the clinical application of vulnerable-plaques detection, but may also provide more information on the pathophysiological changes and pathways involved in the vascular responses after stent implantation.

References

1. Topol E, Nissen S. Our preoccupation with coronary luminology. The dissociation between clinical and angiographic findings in ischemic heart disease. Circulation. 1995;92:2333–42.
2. Little WC, Constantinescu M, Applegate RJ, Kutcher MA, Burrows MT, Kahl FR, et al. Can coronary angiography predict the site of a subsequent myocardial infarction in patients with mild-to-moderate coronary artery disease. Circulation. 1988;78:1157–66.
3. Spears JR, Spokojny AM, Marais HJ. Coronary angioscopy during cardiac catheterization. J Am Coll Cardiol. 1985;6:93–7.
4. Mizuno K, Arai T, Satomura K, Shibuya T, Arakawa K, Okamoto Y, et al. New percutaneous transluminal coronary angioscope. J Am Coll Cardiol. 1989;13:363–8.
5. Sherman CT, Litvack F, Grundfest W, Lee M, Hickey A, Chaux A, et al. Coronary angioscopy in patients with unstable angina pectoris. N Engl J Med. 1986;315:913–9.

6. Uchida Y, Nakamura F, Tomaru T, Morita T, Oshima T, Sasaki T, et al. Prediction of acute coronary syndromes by percutaneous coronary angioscopy in patients with stable angina. Am Heart J. 1995;130:195–203.
7. Takano M, Mizuno K, Okamatsu K, Yokoyama S, Ohba T, Sakai S. Mechanical and structural characteristics of vulnerable plaques: analysis by coronary angioscopy and intravascular ultrasound. J Am Coll Cardiol. 2001;38:99–104.
8. Inami S, Ishibashi F, Waxman S, Okamatsu K, Seimiya K, Takano M, et al. Multiple yellow plaques assessed by angioscopy with quantitative colorimetry in patients with myocardial infarction. Circ J. 2008;72:399–403.
9. Lehmann KG, van Suylen RJ, Stibbe J, Slager CJ, Oomen JA, Maas A, et al. Composition of human thrombus assessed by quantitative colorimetric angioscopicanalysis. Circulation. 1997;96:3030–41.
10. Ishibashi F, Mizuno K, Kawamura A, Singh PP, Nesto RW, Waxman S. High yellow color intensity by angioscopy with quantitative colorimetry to identify high-risk features in culprit lesions of patients with acute coronary syndromes. Am J Cardiol. 2007;100:1207–11.
11. Uchida Y, Uchida Y, Kawai S, Kanamaru R, Sugiyama Y, Tomaru T, et al. Detection of vulnerable coronary plaques by color fluorescent angioscopy. J Am Cardiol Imaging. 2010;3:398–408.
12. Muller JE, Tofler GH, Stone PH. Circadian variation and triggers of onset of acute cardiovascular disease. Circulation. 1989;79:733–43.
13. Falk E. Stable versus unstable atherosclerosis: clinical aspects. Am Heart J. 1999;138:S421–5.
14. Virmani R, Burke AP, Farb A, Kolodgie FD. Pathology of the unstable plaque. Prog Cardiovasc Dis. 2002;44:349–56.
15. Thieme T, Wernecke KD, Meyer R, Brandenstein E, Habedank D, Hinz A, et al. Angioscopic evaluation of atherosclerotic plaques: validation by histomorphologic analysis and association with stable and unstable coronary syndromes. J Am Coll Cardiol. 1996;28:1–6.
16. Isoda K, Satomura K, Ohsuzu F. Pathological characterization of yellow and white plaques under angioscopy. Int J Angiol. 2001;10:183–7.
17. Miyamoto A, Prieto AR, Friedl SE, Lin FC, Muller JE, Nesto RW, et al. Atheromatous plaquecap thickness can be determined by quantitative color analysis during angioscopy: implications for identifying the vulnerable plaque. Clin Cardiol. 2004;27:9–15.
18. Ueda Y, Ohtani T, Shimizu M, Hirayama A, Kodama K. Assessment of plaque vulnerability by angioscopic classification of plaque color. Am Heart J. 2004;148:333–5.
19. Mizuno K, Miyamoto A, Satomura K, Kurita A, Arai T, Yanagida S, et al. Angioscopic coronarymacromorphology in patients with acute coronarydisorders. Lancet. 1991;337:809–12.
20. Wang Z, Inami S, Kirinoki S, Yamamoto H, Takagi G, Aoki S, et al. Angioscopic study of silent plaque disruption in non-ischemic related coronary artery in patients with stable ischemic heart disease. Int Heart J. 2010;51:383–7.
21. Ohtani T, Ueda Y, Mizote I, Oyabu J, Okada K, Hirayama A, et al. Number of yellow plaques detected in a coronary artery is associated with future risk of acute coronary syndrome: detection of vulnerable patients by angioscopy. J Am Coll Cardiol. 2006;47:2194.
22. Saratani K, Iwanaga Y, Hayashi T, Miyazaki S. Impact of plaque color by angioscopic evaluation on long-term clinical outcomes in patients with acute myocardial infarction undergoing percutaneous coronary intervention. Atherosclerosis. 2010;211:170–5.
23. Hayashi T, Kiyoshima T, Matsuura M, Ueno M, Kobayashi N, Yabushita H, Kurooka A, Taniguchi M, Miyataka M, Kimura A, Ishikawa K. Plaque erosion in the culprit lesion is prone to develop a smaller myocardial infarction size compared with plaque rupture. Am Heart J. 2005;149:284–90.
24. Mizote I, Ueda Y, Ohtani T, Shimizu M, Takeda Y, Oka T, et al. Distal protection improved reperfusion and reduced left ventricular dysfunction in patients with acute myocardial infarction who had angioscopically defined ruptured plaque. Circulation. 2005; 112:1001–7.
25. Mizuno K, Satomura K, Miyamoto A, Arakawa K, Shibuya T, Arai T, et al. Angioscopic evaluation of coronary-artery thrombi in acute coronary syndromes. N Engl J Med. 1992;326:287–91.
26. Miuzuno K, Miyamoto A, Isojima K, Kurita A, Senoo A, Arai T, et al. A serial observation of coronary thrombi in vivo by a new percutaneous trans coronary angioscopy. Angiology. 1992;43: 91–9.
27. Yamamoto M, Takano M, Okamatsu K, Murakami D, Inami S, Xie Y, et al. Relationship between thin cap fibroatheroma identified by virtual histology and angioscopic yellow plaque in quantitative analysis with colorimetry. Circ J. 2009;73:497–502.
28. Kawano T, Honye J, Takayama T, Yokoyama S, Chiku M, Chiku M, Ando H, et al. Compositional analysis of angioscopic yellow plaques with intravascular ultrasound radiofrequency data. Int J Cardiol. 2008;125:74–8.
29. Ariani M, Siegel R, Fishbein MC. Histopathologic validation of angioscopy and intravascular ultrasound. Circulation. 1991;84: 109–17.
30. Nasu K, Tsuchikane E, Katoh O, Vince DG, Margolis PM, Virmani R, et al. Impact of intramural thrombus in coronary arteries on the accuracy of tissue characterization by in vivo intravascular ultrasound radiofrequency data analysis. Am J Cardiol. 2008;101:1079–83.
31. Yabushita H, Bouma BE, Houser SL, Aretz HT, Jang IK, Schlendorf KH, et al. Characterization of human atherosclerosis by optical coherence tomography. Circulation. 2002;106:1640–5.
32. Kubo T, Imanishi T, Takarada S, Kuroi A, Ueno S, Yamano T, et al. Implication of plaque color classification for assessing plaque vulnerability: acoronaryangioscopy and optical coherence tomography investigation. J Am Coll Cardiol Interv. 2008; 1:74–80.
33. Takano M, Jang IK, Inami S, Yamamoto M, Murakami D, Okamatsu K, et al. In vivo comparison of optical coherence tomography and angioscopy for the evaluation of coronary plaque characteristics. Am J Cardiol. 2008;101:471–6.
34. Kubo T, Imanishi T, Takarada S, Kuroi A, Ueno S, Yamano T, et al. 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;50:933–9.
35. Strumpf RK, Heuser RR, Eagan JT. Angioscopy: a valuable tool in the deployment and evaluation of intracoronary stents. Am Heart J. 1993;126:1204–8.
36. Takano M, Ohba T, Inami S, Seimiya K, Sakai S, Mizuno K. Angioscopic differences in neointimal coverage and in persistence of thrombus between sirolimus-eluting stents and bare metal stent after a 6-month implantation. Eur Heart J. 2006;27: 2189–95.
37. Oyabu J, Ueda Y, Ogasawara N, Okada K, Hirayama A, Kodama K. Angioscopic evaluation of neointima coverage: Sirolimus drug eluting stent versus bare metal stent. Am Heart J. 2006;152: 1168–74.
38. Sakai S, Mizuno K, Yokoyama S, Tanabe J, Shinada T, Seimiya K, et al. Morphologic changes in infarct-related plaque after coronarystent placement: a serial angioscopy study. J Am Coll Cardiol. 2003;42:1558–65.
39. Ueda Y, Nanto S, Komamura K, Kodama K. Neointimal coverage of stents in human coronary arteries observed by angioscopy. J Am Coll Cardiol. 1994;23:341–6.
40. Yokoyama S, Takano M, Sakai S, Ohba T, Seimiya K, Okamatsu K, et al. Difference in neointimal proliferation between ruptured

and non-ruptured segments after bare metal stent implantation. Int Heart J. 2010;51:7–12.
41. Asakura M, Ueda Y, Nanto S, Hirayama A, Adachi T, Kitakaze M, et al. Remodeling of in-stent neointima, which become thinner and transparent over 3 years: serial angiographic and angioscopic follow-up. Circulation. 1998;97:2003–6.
42. Isner JM, Kearney M, Bortman S, Passeri J. Apoptosis in human atherosclerosis and restenosis. Circulation. 1995;91:2703–11.
43. Yokoyama S, Takano M, Yamamoto M, Inami S, Sakai S, Okamatsu K, et al. Extended follow-up by serial angioscopic observationfor bare-metal stents in native coronary arteries: from healing response to atherosclerotic transformation of neointima. Circ Cardiovasc Interv. 2009;2:205–12.
44. Kotani J, Awata M, Nanto S, Uematsu M, Oshima F, Minamiguchi H, et al. Incomplete neointimal coverage of sirolimus-eluting stents: angioscopic findings. J Am Coll Cardiol. 2006;47:2108–11.
45. Awata M, Kotani J, Uematsu M, Morozumi T, Ohnishi T, Iida O, et al. Serial angioscopic evidence of incomplete neointimal coverage after sirolimus-eluting stent implantation: comparison with bare-metal stents. Circulation. 2007;116:910–6.
46. Takano M, Mizuno K. Late coronary thrombosis in a sirolimus-eluting stent due to the lack of neointimal coverage. Eur Heart J. 2006;27:1133.
47. Awata M, Nanto S, Uematsu M, Morozumi T, Watanabe T, Onishi T, et al. Angioscopic comparison of neointimal coverage between zotarolimus and sirolimus-eluting stents. J Am Coll Cardiol. 2008;52:787–92.
48. Awata M, Nanto S, Uematsu M, Morozumi T, Watanabe T, Onishi T, et al. Heterogeneous arterial healing in patients following paclitaxel-eluting stent implantation: comparison with sirolimus-eluting stents. J Am Coll Cardiol Interv. 2009;2:453–8.
49. Hara M, Nishino M, Taniike M, Makino N, Kato H, Egami Y, et al. High incidence of thrombus formation at 18 months after paclitaxel-eluting stent implantation: angioscopic comparison with sirolimus-eluting stent. Am Heart J. 2010;159:905–10.
50. Takano M, Ohba T, Inami S, Seimiya K, Sakai S, Mizuno K. Angioscopic differences in neointimal coverage and in persistenceof thrombus between sirolimus-eluting stents and bare metal stentsafter a 6-month implantation. Eur Heart J. 2006;27:2189–5.
51. Higo T, Ueda Y, Oyabu J, Okada K, Nishio M, Hirata A, et al. Atherosclerotic and thrombogenic neointima formed over sirolimusdrug-eluting stent: an angioscopic study. J Am Coll Cardiol Imaging. 2009;2:616–24.
52. Whelan DM, van der Giessen WJ, Krabbendam SC, van Vliet EA, Verdouw PD, Serruys PW, et al. Biocompatibility of phosphorylcholine coated stents in normal porcine coronary arteries. Heart. 2000;83:338–45.