Coronary Angioscopic Evaluation for Serial Changes of Luminal Appearance After Pharmacological and Catheter Interventions

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Although preventive pharmacological therapies effectually reduce the risk of cardiovascular events, acute coronary syndrome (ACS) remains a leading cause of morbidity and mortality in our country, Japan. Disruption of atherosclerotic vulnerable plaques and flow-limiting thrombus formation in non-stent segments of native coronary arteries are considered a main mechanism of ACS. In addition, stent thrombosis originating from implanted metallic coronary stents, so-called vulnerable stents, occasionally appears as ACS in the clinical settings. Coronary angioscopy is a unique imaging modality permitting direct visualization of luminal structures, such as atherosclerotic plaque, thrombus, stent struts, and proliferating neointima. On the basis of accumulated angioscopic findings, intense yellow plaques and stents without neointimal coverage are considered vulnerable plaques and vulnerable stents, respectively. In contrast, morphological disappearance of vulnerable plaques or vulnerable stents by pharmacological and trans-catheter therapies imply stabilization of the plaques or stents. Hence, angioscopic assessment for vulnerability (or stability) of atherosclerotic plaques and implanted stents might be useful for risk classification in the future events of ACS. To evaluate serial changes of coronary lumen after pharmacological and catheter interventions using angioscopy might also provide important information on potential benefits and surrogate endpoints of the therapies and on patients' management. (*Circ J* 2010; **74**: 240–245)

Key Words: Angioscopy; Drugs; Plaque; Stents; Thrombus

Fiber-optic coronary angioscope is a catheter-based, intravascular imaging device that has been approved for clinical use in Japan. Angioscopy provides high-resolution, 3-dimensional, and full color images as direct visualization of the coronary lumen, and its images are applicable for macroscopic diagnosis of intracoronary structures, including atherosclerotic plaque, thrombus, and neointimal tissue based on surface color and morphology.¹ In the current review article, vulnerable plaque and vulnerable stent determined by angioscopic findings, and their changes following pharmacological and catheter intervention therapies are discussed.

System and Procedure of Angioscopy

The system of angioscopy consists of an imaging catheter, light source (300 W xenon light), a color monitor, and a recorder. Two types of the angioscopic catheters are available, one is an occlusion type and another type is maintenance of coronary blood flow. The angioscopic catheter is required to remove the blood from the viewing field and to displace the blood with transparent fluid in order to acquire clear angioscopic images. In our institute, the occlusion type

angioscopic catheter (VecMova Neo, FiberTech Co, Chiba, Japan) is used because it can obtain continuous images of the whole vessel wall. This catheter is 4.5-Fr in diameter, rapid-exchanged type and is composed of 2 elements (image bundle in delivery catheter). A guide catheter measuring more than 7-Fr in diameter is needed for angioscopic procedures. The image bundle consists of 3,000 optical fibers with micro-lens at the distal tip, which can be advanced 7 cm in front of the delivery catheter along a 0.014-inch guide wire. A compliant occlusion balloon is located at the distal tip of the delivery catheter and the balloon is inflated manually during the image acquisition. Warmed Ringer lactate is continuously irrigated through the delivery catheter at a rate of 0.5 to 1.0 ml/s by a power injector. Before observation, white balance is adjusted for color correction. Light power is also adjusted to avoid reflection and to obtain images with adequate brightness for determination of the color.^{1,2} In angioscopic analysis, the advantage is the ability to detect coronary thrombus more sensitively than other imaging modalities,³ whereas the largest disadvantage is difficulty in quantitative assessment for color, distance, or volume.

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Figure 1. Classification of coronary plaque. (A) A white plaque (yellow grade 0). (B) A light yellow plaque (grade 1). (C) A medium yellow plaque (grade 2). (D) A dark yellow plaque (grade 3). (E) A complex yellow plaque with mural thrombus formation.

Vulnerable Plaque

The principle cause of acute coronary syndrome (ACS) is disruption of atherosclerotic plaque and subsequent thrombus formation in native coronary arteries.^{4,5} The greatest interest to physicians is to predict and anticipate the culprit plaque of ACS, so-called unstable or vulnerable plaques. In recent years, invasive or non-invasive diagnostic imaging technologies have been therefore developed for identifying vulnerable plaques.^{3,6,7} According to previous pathological and clinical studies, definite vulnerable plaques demonstrate morphological and functional characteristics as follows: (1) active inflammation with infiltration of monocytes, macrophages, or T-lymphocytes; (2) fibrous cap ($\leq 65 \mu\text{m}$) with a large lipid core (thin-cap fibroatheroma: TCFA); (3) endothelial denudation with superficial platelet aggregation; (4) fissured plaque; (5) severe stenosis $>90\%$; (6) superficial calcified nodule; (7) glistening yellow plaque; (8) intraplaque hemorrhage; (9) endothelial dysfunction; or (10) positive remodeling.⁵ Histological TCFA is accounted for 60–70% of the culprit lesion in ACS, and then plentiful energy has been invested in identifying TCFA before suffering from ACS.

On the basis of angioscopic images, plaque is defined as a non-mobile, elevated, and/or protruding structure that can be clearly demarcated from the adjacent vessel wall. Coronary plaque is qualitatively divided into yellow plaque or not (white plaque) according to the surface color. Furthermore, yellow intensity (or grade) of the plaque is classified semi-quantitatively as 0, white; 1, light yellow; 2, (medium) yellow; or 3, dark yellow (Figure 1), or evaluated quantitatively by special software.^{8–16} The majority of yellow plaques are composed of lipid-rich tissue or necrotic core identified by optical coherence tomography (OCT) and radiofrequency intravascular ultrasound (IVUS).^{10–12,17–19} In contrast, white plaque is histological fibrous plaque or lipid plaque with thick fibrous cap.^{11,17–19} Yellow intensity is negatively correlated with fibrous cap thickness, and intense yellow plaque is corresponded to TCFA.^{11,18,19} Furthermore, yellow plaque is associated with the prevalence of positive remodeling and thrombus formation.^{13,20} Disruption of intense yellow plaque and thrombus are frequently observed at the culprit lesion in patients with ACS.^{2,21–23} Moreover, prospective studies demonstrate that patients having glistening or intense yellow plaques show higher incidence of ACS in comparison to those without yellow plaques.^{24,25} These facts indicate that yellow plaque identified by angioscopy, especially intense or glistening yellow plaque might have potential vulnerability and be at high risk of cardiovascular events in the future.

Vulnerable Stent

Since catheter intervention procedures for ischemic heart disease innovate using drug-eluting stents (DES), ACS due to very late stent thrombosis (VLST), occurring in an unexpected period of >1 year after stent implantation, has become a major clinical issue.²⁶ Recently, a new concept of “vulnerable stent” has been advocated as well as the existent notion about vulnerable plaque, vulnerable blood, vulnerable myocardium, and vulnerable patients.^{27,28} Pathological and morphological mechanism of VLST in DES is mainly attributed to lack of re-endothelialization as delayed vascular healing response, excess of fibrin deposition, and acquired incomplete stent apposition.^{29–31} On one hand, neointima mainly composed of vascular smooth muscle cells almost completely cover the stent within a few months following conventional bare-metal stents (BMS) deployment.^{2,9,29,32–35} Intracoronary high-resolution images by angioscopy or OCT probably are powerless to distinguish fibrin layer from thin neointimal membrane and to validate re-endothelialization in living patients.^{9,36–39} However, part of the uncovered (exposed) stent or stent without neointimal coverage might be equivalent to vulnerable stent.^{27,40} It is uncertain whether stent containing latent thrombus directly links with the future occurrence of VLST and becomes vulnerable stent.

Changes After Pharmacological Intervention

To date, a few sorts of lipid-lowering drugs have been utilized for serial angioscopic evaluation.^{8,16,41–43} The culprit plaque of ACS or ischemia-related plaque with severe stenosis is usually treated by catheter intervention. Although disrupted and thrombotic yellow plaque is located in not only the culprit lesion, but also non-culprit lesion showing no significant stenosis on the angiograms,^{8,41–44} such angioscopically vulnerable plaque generally receives pharmacological intervention. Non-culprit plaques are therefore selected as targets for angioscopic analysis in the assessment of pharmacological intervention. Administration of atorvastatin for 12 months significantly reduces yellow color grade and complexity of the non-culprit plaque, and the changes in yellow grade are correlated with variation of serum low-density lipoprotein concentration.⁸ A similar phenomenon is recognized after 6-month follow-up of bezafibrate therapy without any angiographic regression on the target plaques.⁴¹ In control participants receiving only diet therapy, the angioscopic scores are unchanged or increased.^{8,41} Statin therapy also has favorable potency for healing over subclinical ruptured plaque in non-culprit lesions (Figure 2).⁴² A serial combination study using

Figure 2. Serial changes in non-culprit plaques by pharmacological intervention. (A) Yellow plaque intensity clearly reduces following 12-month statin therapy. (B) Statin therapy heals up thrombotic yellow plaque.

Figure 3. Classification of neointimal stent coverage and in-stent thrombus. (A) Stent struts without neointimal tissue (uncovered struts). (B) Struts with a thin neointimal layer (visible struts). (C) Struts of complete neointimal coverage (invisible struts). (D) In-stent thrombus.

angiography and IVUS shows that early loss of yellow color and subsequent plaque volume reduction are invited by atorvastatin.⁴³ The mechanisms of the changes in plaque appearance (color and morphology) are speculated that statins increase collagen content (fibrous cap thickness) and decrease lipid content.^{8,45} These results suggest that lipid-lowering drugs alter plaque composition and then lead to plaque stabilization. Although randomized IVUS trials reveal amlodipine and pioglitazone, which are antihypertensive agent and insulin sensitizer respectively, inhibit progression of atherosclerotic plaque,^{46,47} there is no angiographic evidence for the effects of these medicines on vulnerable plaques.

Changes After BMS Implantation

Numerous angiographic reports about short- to long-term follow-ups have described for the features within the BMS segments.^{2,9,32–34,48–52} neointimal stent coverage (NSC) is often semi-quantitatively categorized in the similar manner of plaque color (Figure 3). Immediately and approximately 2 weeks after BMS implantation, no structures covering the struts of BMS are found in any cases.^{2,9,32} Partial NSC is commonly observed at 1-month follow-up.² At around 2- to 6-month follow-ups, proliferating neointima with a smooth and white surface buries the struts and the majority of struts become invisible.^{2,9,32–34,48–50} Although experimental animal models show perfection of NSC within a few weeks, angiographic findings suggest sufficient NSC on advanced athero-

sclerotic plaques in human coronary arteries requires at least a few months of time. In patients with ACS, residual in-stent thrombus is seen at 92% of 1-month follow-up and decreases to 13% at 6 months.² The generality of thrombi within the BMS segments disappear and NSC nearly accomplishes until 6 months.^{2,9,32–34,48–50} In proportion to growth of white neointima, yellow intensity of the culprit plaque observed through the struts has been reduced.^{2,9,52} In-stent restenosis (ISR) caused by excessive neointimal hyperplasia, the Achilles' heel of the intervention with BMS, sometimes limits its clinical success. Nevertheless, adequate neointimal coverage over the struts and underlying vulnerable plaque might eradicate vulnerable stent and play a key role in plaque stabilization of the short-term.

A long-term serial study discloses that non-transparent white neointima of 6-month becomes transparent with angiographic regression (neointimal thinning) at 3-year follow-up.⁴⁸ At this phase, any in-stent thrombi are not found. There is a speculation that qualitative and quantitative remodeling of neointima might be caused by decrease in cellular components and apoptosis.⁵³ In a further long-term (≥ 4 years) follow-up study, appearance of yellow plaque is documented and the atherosclerotic transformation of neointima is closely correlated with late luminal narrowing on the coronary angiography.⁵⁰ In 31% of the study population, yellow plaques have complex morphology and thrombus and they are similar to vulnerable plaques at the culprit lesion of ACS. Chronic inflammation due to foreign body reaction to the

Figure 4. Serial changes in culprit plaques by catheter intervention. (A) White neointima completely covers over a bare-metal stent at 6-month follow-up. Yellow plaque, thrombus, and struts observed immediately after stent implantation disappear from the view. (B) Yellow plaque, residual thrombus, and struts of a drug-eluting stent are found at 6-month follow-up. Stent struts have incomplete neointimal coverage.

metallic stent or expansion of neovascularization from peristrut to intra-intima might contribute to the formation of lipid-laden plaque with vulnerability,^{54,55} and neointima of BMS is not static but dynamic material. Moreover, ruptured yellow plaque and thrombus formation is found in a case of VLST derived from the BMS segment.⁵¹ Although VLST of BMS is thought to arise from persistent uncovered struts, diffuse ISR, and disrupted plaque outside the stent,^{51,56} in-stent vulnerable plaque built up in the extended late phase might be one of the potential causes of VLST after BMS implantation.^{50,55}

Changes After DES Implantation

Recent utilization of DES dramatically reduces the incidence of ISR and target lesion revascularization in comparison to BMS era despite unresolved problem with VLST that is increasing steadily.⁵⁷ It is expected that angioscopy illuminates inside the DES and the presence of vulnerable stent beyond angiographic and IVUS estimation. Plenty of observational examinations focusing on NSC after DES implantation by use of angioscopy have been released from Japan.^{9,33,34,39,40,58–67} The common findings of the reports are that NSC of first-generation DES, sirolimus-eluting stents (SES) and paclitaxel-eluting stents, is obviously inhibited in comparison to that of BMS.^{9,33,34,60} In a next-generation DES, zotarolimus-eluting stents, more adequate NSC of short-term follow-up is achieved than in SES.^{67,68} As pathological researches points out,^{30,69} delayed NSC is remarkably found in stent overlapping segments.^{9,59,60} NSC within the DES segments progresses heterogeneously^{39,58} and incomplete NSC (or uncovered stent struts) persists for up to 2 years.^{40,52,66} Furthermore, lack of association between advanced neointimal growth and relatively high prevalence of thrombus compared with BMS suggests that neointimal tissue of DES might have immature endothelial function and might be abnormal tissue.^{38,39} On the basis of these results, several investigators therefore recommend long-term dual antiplatelet therapy for prevention against VLST.

With regard to thrombus, in-stent thrombus frequently remains in short-term^{9,33,34} and sometimes persists at 2-year follow-up.^{52,66} In addition, new thrombus formation associated with the presence of uncovered struts is documented in

spite of continuous dual antiplatelet therapy.^{52,66} Incomplete NSC and extremely thin neointimal layer might have less influence on the appearance of yellow plaque that is located outside the DES, while thick white neointima of BMS extinguishes yellow plaque from the view (Figure 4). However, a few investigators report about increasing yellow intensity of the plaque and occurrence of thrombogenic yellow neointima within the DES segment.^{9,63–65} Although the precise mechanisms are uncertain, vascular response to DES including inflammatory or atherosclerotic process might absolutely differ than that of BMS. Furthermore, angioscopic thrombus relevant to uncovered struts or yellow plaque (neointima) is subclinical and has no direct linkage with development into VLST. It is understood that multiple factors, such as lack of re-endothelialization (presence of uncovered struts), coronary flow impairment, and increased blood thrombogenicity cause VLST of DES. Therefore, only the presence of uncovered struts might not be the predictor of VLST. Macroscopic evaluation of uncovered struts by angioscopy does not reflect absence of re-endothelialization and is overestimated because of limited image resolution of angioscopy.^{39,62} Nevertheless, conditions of vulnerable stent and vulnerable plaque determined by angioscopy continue for a long time after implantation of first-generation DES.

Changes After Other Catheter Interventions

Following intracoronary brachytherapy for ISR, intracoronary lumen is observed by angioscopy.^{70,71} Uncovered struts, eroded or ulcerated neointima, and mural thrombus are found for up to 9 months. Thrombus formation and uncovered struts are also seen 9 months after deployment of polytetrafluoroethylene-covered stent (stent graft) that is applied to coronary perforation or a giant coronary aneurysm.⁷² Delayed arterial healing response characterized by incomplete NSC and presence of uncovered stent struts is not specific to the catheter intervention with DES.

Conclusions

To detect morphological vulnerable plaque and vulnerable stent using angioscopy is not coordinate with veritable prediction of ACS and VLST. Nevertheless, angioscopic evaluation

for serial changes in lumen appearance after pharmacological and catheter interventions might provide important information on potential benefits and surrogate endpoints of the therapies and on patients' management. In the future, prospective large-scale studies and application of new technologies, such as molecular imaging, could open the door to identifying genuine vulnerable plaque and vulnerable stent.

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