Coronary Paque Imaging by Coronary Angioscopy

—Comparison with the Other Modalities—

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The recent improvement of technical aspects of multimodality coronary imaging allow not only assessment of the degree of vessel luminal narrowing but also evaluation of the plaque characteristics and the useful prognostic information and accurate risk stratification. Among them, coronary angioscopy is the coronary imaging modality that enables direct visualization of internal surface of a vessel. Moreover it provides the detail information of plaque morphology, thrombus formation and neointimal coverage (NIC) after stent implantation. A lot of previous studies have shown that coronary angioscopy enabled not only the detection of vulnerable plaque but also prediction of cardiovascular events and percutaneous coronary intervention related complications. In this review, we discuss the role of coronary angioscopy for coronary plaque imaging, including in a comparison with other currently available imaging modalities used to examine atherosclerotic plaque.

Key words: coronary angioscopy, vulnerable plaque, coronary imaging

Introduction

For more than decades, conventional invasive coronary angiography has been the gold standard for the diagnosis of coronary artery disease and clinical decision making for percutaneous coronary intervention (PCI). However, coronary angiography has several limitations, including the substantial interpretation variability of visual estimates and assessment of lesion severity for diffuse atherosclerotic lesions and intermediate-severity lesions.^{1,2)} The recent improvement of technical aspects of multimodality coronary imaging allow not only assessment of the degree of vessel luminal narrowing but also evaluation of the plaque characteristics and the useful prognostic information and accurate risk stratification. Among them coronary angioscopy is the coronary imaging modality that enables direct visualization of internal surface of a vessel. Moreover it provides the detail information of plaque morphology or thrombus formation.^{3,4)} A lot of previous studies have shown that coronary angioscopy enabled not only the detection of vulnerable plaque but also prediction of cardiovascular events and percutaneous coronary intervention related complications.

In this review, we discuss the role of coronary angioscopy for coronary plaque imaging, including in a comparison with other currently available imaging modalities used to examine atherosclerotic plaque.

Coronary Angioscopy

Coronary angioscopy enables direct visualization of internal surface of a vessel and provides the detail information of various plaque morphology or thrombus formation.^{3,4)} Coronary plaques are assessed based on the surface color and characteristics. Plaque color is classified as white, light yellow, yellow (medium yellow) or intensive yellow (dark yellow)^{4,5)} (Fig. 1A). Yellow plaques of higher color grade is strongly related with the positive remodeling, thrombus formation and thin-cap fibroatheroma (TCFA) and considered high-risk plaque,^{5–8)} whereas white plaques correlate fibrous plaque or pathological intimal thickening and is considered as stable plaque.⁹⁾ Coronary angioscopy also has the ability to visualize intraluminal thrombus for high sensitivity and specificity,¹⁰⁾ and angioscopic thrombus is classified as red, white or mixed thrombus¹¹⁾ (Fig. 1B). Furthermore this modality allows evaluation of neointimal coverage (NIC) after stent implantation and NIC was classified into 3 or 4 grades^{12,13)} (Fig. 1C). In particular coronary angioscopy was the first imaging modality that enabled direct visualization of neo-atherosclerosis after drug-eluting stent (DES) implantation.¹⁴⁾

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Fig. 1A Yellow color grade of plaque. Plaque color is classified as white, light yellow, yellow or intensive yellow according to the surface color.

Fig. 1B Thrombus. Angioscopic thrombus is classified as red, white or mixed thrombus according to the color.

Fig. 1C Neointimal coverage grade. grade 0 = no coverage by neointima; grade 1 = coverage by a thin layer of neointima; grade 2 = complete coverage by neointima.

NIC at 1 year after 2nd-generation DES implantation was more homogeneous with white and less thrombus than that after 1st-generation DES.¹³⁾ Another study showed in-stent yellow plaque at 1 year after DES implantation was associated with cardiovascular event.¹⁵⁾

According to the reports of histopathologic validation of coronary angioscopy, yellow plaque had a thinner fibrous cap and a larger lipid core area compared to the white plaque.¹⁶⁾ Furthermore Uchida et al. investigated the association yellow plaque with collagen fiber and reported that majority of glistening yellow plaque by coronary angioscopy were composed of scanty collagen fiber, which means less-protected plaques against mechanical stress.¹⁷⁾ Therefore the glistening yellow was considered as vulnerable plaque. Recently Shibuya et al. investigated the relationship between angioscopic plaque features and histological atherosclerotic characteristics.⁹⁾ They showed that 95% of dark yellow plaque was categorized by histological analysis as fibrocalcific plaque, fibroatheroma, or TCFA, generally considered to be advanced plaque.

Other Imaging Modalities for Vulnerable Plaques Comparison with Coronary Angioscopy

1. Intravascular ultrasound (IVUS)

Intravascular ultrasound (IVUS) provides real-time with

cross-sectional images of the examined vessel perpendicular to the longitudinal axis of the catheter. Gray-scale IVUS enables accurate measurements of lumen and vessel diameters, morphology, and severity of the atherosclerotic plaque. Attenuated plaque,^{18,19)} the presence of positive remodeling^{20,21)} and spotty calcification^{19,22)} are considered as a feature of vulnerable plaque detected by gray-scale IVUS. Histopathologically, attenuated plaques corresponded to a fibroatheroma with a necrotic core or pathological intimal thickening with a lipid pool, and spotty calcification is closely related to the presence of a necrotic core.¹⁹⁾ Coronary plaque with positive remodeling had a higher lipid content and macrophage count,²⁰⁾ which indicated plaque vulnerability.

However, gray-scale IVUS has significant limitations in assessing plaque composition, and radiofrequency-derived histopathological analysis by IVUS may provide quantitative information on plaque composition.

Virtual histology (VH)-IVUS provides quantitative information on plaque composition and characterizes atherosclerotic plaque as fibrous, fibro fatty, dense calcium, and necrotic core.²³⁾ Several studies have demonstrated larger amounts of necrotic core and VH-IVUS-derived thin-cap fibroatheroma (VH-TCFA), in patients with acute coronary syndrome, compared with those with stable angina.^{24,25)} VH-TCFA has been defined as a necrotic core $\geq 10\%$ of plaque area at either the minimal lumi-

Fig. 2 Representative images of white plaque and high-grade yellow plaque. A, B and C showed the gray scale IVUS, VH-IVUS and angioscopic images of the white plaque. D, E and F showed the same images of the high-grade yellow plaque respectively. There is a significant relationship between angioscopic yellow color intensity and mean percentage of necrotic core determined by VH-IVUS. IVUS: intravascular ultrasound; VH:virtual histology. Reprinted with permission from Kawano T et al.³⁵⁾

nal area site or the largest necrotic core site in ≥ 3 consecutive frames without evident overlying fibrous tissue in the presence of $\geq 40\%$ plaque burden.²⁴⁾ The PROSPECT²⁶⁾ and VIVA study²⁷⁾ using VH-IVUS have shown that non-culprit lesions associated with adverse cardiovascular events were more likely to be characterized by a large plaque burden, a narrow luminal area or VH-TCFA. Recently, ATHEROREMO-IVUS study demonstrated that the presence of VH-TCFA in non-culprit lesion was independently associated with the composite of acute coronary syndrome (ACS) or death only.²⁸⁾ Moreover in elective PCI, VH-IVUS has demonstrated that large necrotic cores related to distal embolization.²⁹⁾

Integrated backscatter (IB)-IVUS, which provides two-dimensional color-coded maps for the tissue characterization of coronary plaques, classifies plaque components into 4 categories; calcification, fibrous, dense fibrosis and lipid pool.³⁰⁾ Previous studies showed that not only culprit lesions but also non-culprit lesions in ACS are significantly increased in lipid component and decreased in fibrous component compared with those with stable angina pectoris (SAP).^{31,32)} In elective stent implantation, Uetani et al. reported that a larger plaque volume and lipid-rich plaque were independent predictor of periprocedural myocardial injury (PMI).³³⁾

In the reports that compared the IVUS with the coronary angiography for the vulnerable plaque, Takano et al. have shown

that yellow plaque is associated with increased distensibility and positive remodeling.⁸⁾ They also demonstrated that the angioscopic yellow plaque was strongly correlated with VH-TCFA.³⁴⁾ Another VH-IVUS analysis showed that the amount of necrotic core was significantly larger in Grade 2 and Grade 3 yellow plaque than white plaque³⁵⁾ (Fig. 2). IB-IVUS analysis revealed that the surface color of plaques in coronary angiography reflected the thickness of the fibrous cap rather than the size of the lipid core.³⁰⁾ However, VH-IVUS or IB-IVUS have some limitations in assessing thrombus compared to coronary angiography because they can't detect thrombus precisely. Therefore, they may not sufficiently evaluate plaque morphology in ACS.

2. Optical coherence tomography (OCT)

Optical coherence tomography (OCT) is a high-resolution method for imaging plaque characteristics (approximately 10- μm resolution), so it is able to identify precise plaque characterization including fibrous cap thickness, lipid content, ruptured plaque, erosion, calcified nodules, and thrombi.³⁶⁾ In particular OCT-derived TCFA is an important feature of vulnerable plaque. TCFA is characterized by a necrotic core covered by fibrous cap with a thickness $< 65\ \mu\text{m}$, containing rare smooth muscle cells but numerous macrophages, and often increased number of intraplaque vasa vasorum.³⁷⁾ However OCT has some limitation in evaluating total plaque volume or vessel remodel-

Fig. 3A In the angioscopic images, plaque color was graded as white (A-1), light yellow (B-1), yellow (C-1), or intensive yellow (D-1). A lipid pool (*) was characterized by a signal-poor region, and it was semiquantified as the number of involved quadrants on the cross-sectional OCT image (A-2, B-2, C-2, D-2). The fibrous cap was identified as a signal-rich region between the coronary artery lumen and inner border of lipid pool in the OCT image, and its thickness was measured at the thinnest part (A-3, B-3, C-3, D-3; arrows). OCT: optical coherence tomography. Reprinted with permission from Kubo T, et al.⁶⁾

Fig. 3B There was a significant negative correlation between yellow color intensity and fibrous cap thickness. Reprinted with permission from Kubo T, et al.⁶⁾

ing because of its limited ranging depth.

Jang et al. demonstrated that the fibrous cap thicknesses were significantly thinner and the frequency of TCFA were significantly higher in patients with acute myocardial infarction (AMI) and ACS compared with those with stable angina (47 m, 54 μm and 103 μm, respectively), (72%, 50% and 20%, respectively).³⁸⁾

Moreover Ino et al. showed that the fibrous cap thickness was significantly thinner in ST-segment elevation myocardial infarction (STEMI) than that in non ST-segment elevated ACS ($55 \pm 20 \mu\text{m}$ vs $109 \pm 55 \mu\text{m}$) and TCFA were more often seen in STEMI compared with non ST-segment elevated ACS (78% vs 49%).³⁹⁾ In patients treated with elective stent implantation, Lee and Yonetsu et al. have shown that the presence of OCT-defined TCFA can predict post-PCI myocardial injury (52% vs 12%) and (46% vs 16%), respectively.^{40,41)}

Macrophages infiltration in coronary plaque is considered as a feature of vulnerable plaque.^{37,42)} OCT is considered to enables the quantification of macrophages accumulation within fibrous cap as signal-rich region that exceed the intensity of background speckle noise.^{36,43)} Macneill et al. demonstrated that the patients with STEMI and ACS had a significantly greater macrophage density in culprit lesion than those with SAP.⁴⁴⁾ Kato et al. demonstrates that macrophage infiltration was more frequent in ACS patients than in non-ACS patients (82.4% vs. 37.9%).⁴⁵⁾ The presence of microchannel formation⁴⁶⁾ and cholesterol crystals^{47,48)} are also known to be markers of plaque vulnerability, which are detectable in OCT.

In the reports that compared the OCT with the coronary angioscopy for the vulnerable plaque, Kubo et al. have shown that there was a significant negative correlation between yellow color grade and fibrous cap thickness ($p < 0.0001$) and 80% of intensive yellow plaques were thin cap fibroatheroma with a cap thickness of $\leq 65 \mu\text{m}$ in the patients with ACS (Fig. 3).⁶⁾ Takano et al. also demonstrated negative correlation between yellow color grade and the fibrous cap thickness (grade 0 $218 \pm 89 \mu\text{m}$, grade 1 $101 \pm 8 \mu\text{m}$, grade 2 $72 \pm 10 \mu\text{m}$, and grade 3 $40 \pm 14 \mu\text{m}$; $p < 0.05$). The sensitivity and specificity of the coronary angioscopy-identified yellow plaque for having a thin fibrous cap were 98% and 96%, respectively.⁷⁾

3. Computed tomography (CT)

Coronary computed tomography angiography (CCTA) is a promising technique for non-invasive coronary angiography. With the improvement in the technical aspects of CCTA, it is possible not only to detect coronary artery stenosis but also to evaluate plaque characteristics including identification of the vulnerable plaque.⁴⁹⁾

Motoyama et al showed that the CT characteristics of plaques associated with ACS include positive remodeling (PR), low attenuation plaque (LAP), and spotty calcification.⁵⁰⁾ Our study demonstrated that a LAP (CT attenuation value < 55 Hounsfield units), PR (remodeling index > 1.05) and spotty calcification were significant predictors of PMI in SAP; the presence of all 3

CT characteristics showed a high positive predictive value (PPV) of 94%, and their absence showed a high negative predictive value (NPV) of 90%⁵¹⁾ (Fig. 4). The ring like enhancement and napkin-ring sign (NRS) are one of the vulnerable coronary plaque morphologies, characterized by a necrotic core with low-CT attenuation surrounded by a rim of high-CT attenuation, potentially representing TCFA.^{52,53)} Nakazawa et al. reported that patients who experienced transient no-reflow during PCI had ring-like enhancement in culprit lesion.⁵⁴⁾ Otsuka et al. demonstrated that NRS on CCTA was strongly associated with future ACS events compared with those without a NRS.⁵⁵⁾ These findings [PR, LAP, NRS, or spotty calcification] on CCTA are important feature of vulnerable plaque, and presence of them increased the likelihood of ACS, independent of significant coronary artery disease and clinical risk assessment.⁵⁶⁾

In the reports that compared the CCTA with the coronary angioscopy for the vulnerable plaque, Komatsu et al. showed that good correlation between soft plaque detected by CCTA and angioscopic yellow plaque.⁵⁷⁾ Nishio et al. analyzed detection of disrupted plaques by CCTA compared with coronary angioscopy.⁵⁸⁾ This report demonstrated that higher-color-grade yellow plaques and disrupted yellow plaques had a significantly higher incidence of CCTA findings of LAP, PR and NRS. PPV and NPV for the combined coronary CT findings (LAP, PR and NRS) to detect disrupted plaque were 90% and 58%, respectively.

Fig. 4 The CT characteristics of a culprit lesion in the 52 years old male patient with post-PCI troponin T elevation greater than 3 times of normal limit. Coronary angiogram (A) and multiplanar reconstructed image (B) shows severe stenosis in the mid right coronary artery. Cross-sectional images show the proximal reference (C), culprit lesion (D), and distal reference (E). Red circle indicates area of spotty calcification. The lesion has positive remodeling (its remodeling index: 1.28), spotty calcification, and low CT density (16 HU). CT: computed tomography; HU: Hounsfield units. Reprinted with permission from Watabe H, et al.⁵¹⁾

Fig. 5 Representative case of high-intensity plaque. (A) T1-weighted magnetic resonance imaging of high-signal intensity of the right coronary artery with a plaque to myocardium signal intensity ratio of 3.09 (yellow arrow indicates lesion). (B) A coronary angiogram showing severe stenosis in the proximal portion of the right coronary artery. (C) Gray-scale intravascular ultrasound image showing ultrasound attenuation. (D) Integrated backscatter intravascular ultrasound showing lipid-rich plaque (blue area). Reprinted with permission from Hoshi T, et al.⁶³⁾

4. Magnetic resonance imaging (MRI)

Recently non-contrast T1-weighted imaging (T1WI) has emerged as a novel non-invasive imaging modality when searching for vulnerable coronary plaque and high intensity plaque (HIP) detected on non-contrast T1WI has been considered to be vulnerable coronary plaque.^{59–63)} HIP was defined as plaque with higher plaque to myocardium signal intensity ratio (PMR),⁵⁹⁾ which was calculated as the signal intensity of the coronary plaque divided by the signal intensity of the left ventricular muscle near the coronary plaque.

In comparison with MDCT, IVUS and MR images of coronary arteries, Kawasaki et al. demonstrated that coronary HIP was associated with ultrasound attenuation, positive remodeling, remarkably low CT density, and a high incidence of slow flow phenomena.⁵⁹⁾ Another studies have shown that HIP on T1WI related to the presence of coronary thrombus detected by coronary angiography (CAG) or OCT.^{60,61)} Furthermore Noguchi et al. reported that the presence of HIP was a significant predictor of future coronary events in patients with suspected or known coronary artery disease (CAD).⁶²⁾ Recently we reported the association between the presence of HIP and the incidence of myocardial injury. In this study we showed HIP was associated with the characteristics of ultrasound attenuation and PR on IVUS, and $PMR \geq 1.4$ was a significant predictor of PMI in multivariate analysis⁶³⁾ (Fig. 5). According to previous studies HIP is considered to indicate an intraplaque haemorrhage, a lipid-rich necrotic core, a thrombus containing methemoglobin. However histological validation of coronary plaque with HIP have not been evaluated. And there have been no reports that compared the HIP on non-contrast T1WI with the coronary angiography for the vul-

nerable plaque. Therefore these studies may have the possibility to clarify characteristics of HIP.

Prediction of Cardiovascular Event by Coronary Angioscopy

1. Prediction of progression to ACS or occurrence of cardiovascular event (CVE)

In prospective follow-up study in 157 patients with SAP observed by coronary angioscopy, acute coronary syndromes were occurred more frequently in patients with glistening yellow plaques than in those without glistening yellow plaques.⁶⁴⁾ Another prospective study, which followed 552 patients who received catheterization and angioscopic examination for the diagnosis of coronary artery disease, showed that patients with multiple yellow plaques have higher risk of suffering ACS than that without yellow plaque.⁶⁵⁾ Ueda et al. demonstrated in the DES-NOTE study that coronary angioscopy-verified in-stent yellow plaque at 1 year after DES implantation was associated with cardiovascular event (CVE) defined as cardiac death, myocardial infarction, unstable angina, or target lesion revascularization.¹⁵⁾ The incidence of CVE was significantly higher in the patients with yellow plaque than in those without yellow plaque during the periods of 1558 ± 890 days (8.1% vs 1.6%, $P = 0.02$), and the presence of in-stent yellow plaque was revealed as a predictor of CVE. Furthermore recent study, which investigated the relationship between the degree of atherosclerotic changes in the descending thoracic aorta and the coronary artery using coronary angioscopy, showed the angioscopic progression of aortic atherosclerosis is closely associated with vulnerability to and the extent of coronary stenosis.⁶⁶⁾

2. Prediction of PMI

In patients with non-ST-elevated-ACS who underwent pre-interventional coronary angioscopy at the culprit lesions, the presence of coronary angiography derived thrombus was to be the only independent factor associated with elevated troponin T levels before catheterization.⁶⁷⁾ Another study following elective coronary stenting in 42 consecutive patients with SAP showed that coronary angioscopy derived intensive yellow culprit plaque coloration was closely associated with PMI and coronary flow complications.⁶⁸⁾ Moreover recent study, which investigated the occurrence of PMI in 72 in stent restenosis lesion with SAP, demonstrated that PMI lesions had higher frequencies of coronary angioscopy derived intensive yellow neointima, neointima with complex surface, and coronary angioscopy derived atheromatous appearance (CAS-AAP), compared to lesions without PMI.⁶⁹⁾ Multivariate logistic regression analysis identified CAS-AAP (odds ratio: 3.568, 95% confidence interval: 1.109–11.475, $P = 0.033$) as an independent predictor of PMI.

Conclusion

A lot of studies have shown that coronary angioscopy enabled the detection of vulnerable plaque and prediction of not only cardiovascular events but also PCI related complication such as slow/no flow phenomenon or PMI. However coronary angioscopy has several limitations, including the only visualization of the coronary luminal surface, necessity to remove blood from the visual field and difficulty of quantitative evaluation. Therefore we hope the advances in technology will overcome these limitations and expand its clinical use. Moreover further large studies will be expected to determine the clinical impact of coronary angioscopy.

Disclosure Statement

No authors have real or perceived conflicts of interest.

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