Plaque Evaluation by Coronary CT Angiography

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Coronary CT angiography (CCTA) is the most promising, noninvasive tool that allows the visualization of plaque morphology. Plaque morphology characterized by positive remodeling, low attenuation plaque and napkin-ring sign in CCTA has been regarded as rupture-prone vulnerable plaques which account for about 60% of all vulnerable plaques and cause plaque rupture. Currently, importance of stenosis level and plaque volume for vulnerable plaque assessment has been recognized. CCTA is also useful from viewpoint of these evaluations. However, it is considered that evaluation by using CT number that is one of important factors of plaque evaluation is affected various factors. There remain several problems in objectivity and quantitative evaluation. Recently, we developed a novel method for evaluating characteristics of plaque in more objective and quantitative way and reported the usability. Moreover, it may be possible to diagnose vulnerable plaque more correctly by comprehensive evaluation on addition to evaluation of fractional flow reserve and endothelial shear stress using CCTA. In the future, it is expected construction of evidence in multi-center large-scale clinical trial and development of new evaluation method such as molecular CT imaging.

I. The Role of Noninvasive Imaging for Diagnosis of Vulnerable Plaque

Acute coronary syndromes (ACS) often occurs suddenly without precursor symptom.1, 2 It is one of the important challenge for cardiologists to predict and prevent ACS. However, there is no method established. ACS is caused mainly by occlusion of thrombus. So, it is important to identify plaque that causes thrombotic occlusion at high rates (i.e., vulnerable plaque) to solve this problem. Braunwald mentioned that Framingham risk score was insufficient in stratification of ACS onset. He expected to find higher risk group that onset ACS by 15% or more within one year by noninvasive vulnerable plaque imaging. He also predicted that very high risk group that onset ACS more than 25% a year by invasive imaging.3

Various types of vulnerable plaques have been reported.4 In histopathological study of coronary lesion accompanying thrombus that causes ACS, rupture accounts for 55–60%, erosion accounts for 30–35%, and calcified nodule accounts for 3–7%.5 Rupture-prone vulnerable plaque that accounts for about 60% is recognized as thin-capped fibroatheromas (TCFA). It is one of the most important targets of vulnerable plaque imaging. Until now, it has been reported the characteristics of rupture-prone vulnerable plaque include positive remodeling, plaque accounting for 50% more of cross section of vessel area, necrotic core accounting for 25% or more of plaque, vasa vasorum existing in plaque, fibrous cap thickness of 65 μ or less, macrophage infiltrated in fibrous cap and expression of MMP.4 Recently, Narula, et al. analyzed useful index for vulnerable plaque by imaging for 295 plaques (105 stable plaque, 88 TCFA, 102 ruptured plaque) of 213 patients from cardiac sudden death using hierarchical analysis.7

As a result, the most important elements that discriminated plaque characteristics were thickness of fibrous cap, fibroatheroma (almost always >85 μm), ruptured plaques (<55 μm) and TCFA (between 55 and 85 μm). However, clinically, the thickness of fibrous cap can be measured only by optical coherence tomography (OCT). If this element is excluded, level of macrophage inflammation and necrotic core size were useful for discriminating vulnerable plaque in analysis. Although ACS were supposed to develop by rupture irrespective of significant stenosis of plaque, in 70% of ruptured plaque, cross-sectional area showed >75% and only about 5% showed stenosis of <50%. In TCFA, about 40% showed cross-sectional area >75% and only 10% showed <50%. It is arguable whether disassociation of stenosis level distribution of ruptured plaques and TCFA is caused by rapid increase of plaque before rupture or TCFA with higher stenosis level has higher risk. Anyway, it was suggested that not only plaque characteristics evaluation but also plaque volume and stenosis level were important for identification of vulnerable plaque.

In PROSPECT study where future cardiac event for non-culprit lesions of ACS patients whose revascularization was successful was studied prospectively using virtual histology intra-
vascular ultrasound (VH-IVUS), TCFA on VH-IVUS, large plaque burden (≥70%) and reduced minimal lumen area (≤4.0 mm²) were event predictive factors. Also in clinical study, importance of plaque characteristics, plaque volume and stenosis level in vulnerable plaque diagnosis were demonstrated. Additionally, diameter stenosis of plaque that caused cardiac event increased from 32% (observation average) to 65% at follow-up before event. By this, it was supposed that vulnerable plaque rapidly progresses at least until event onset. Meanwhile, VH-IVUS is an invasive modality. So, it cannot be used for screening many patients. By optical medical therapy, onset of cardiac death, cardiac arrest and AMI was 1% of all patients during three years of PROSPECT study. It was realized that patients with such vulnerable plaque should be screened in early stage by noninvasive imaging to stratify them and optimal medical therapy should be performed in the future.

Coronary computed tomography angiography (CCTA) can evaluate not only stenosis level but also plaque characteristics evaluation in coronary artery. It is expected as a tool for imaging vulnerable plaque noninvasively. In the present study, current status of plaque evaluation by CCTA, problems and future perspectives are reviewed.

II. CT Verified Vulnerable Plaque

In vulnerable plaque diagnosis, evaluation of characteristics of plaque is important. So, plaque characteristics evaluation based on CT attenuation value has been reported in CCTA. Motoyama, et al. reported that CT values of plaque judged as soft, fibrous and calcified by IVUS were 11±12 HU, 78±21 HU, and 516±198 HU respectively for 98 plaques in 37 patients using 0.5 mm slice MDCT. They concluded that CT value of soft plaque should be 30 HU or less. Based on this result, they reported that culprit lesion of ACS in CCTA compared to that of stable angina is significantly characterized by microcalcification, positive remodeling (remodeling index >1.1) and low CT value (CT <30 HU). Kashiwagi, et al. compared CCTA performed with optical coherence tomography for the detection of TCFA. Findings on CCTA that were predictive of TCFA were positive remodeling, low-attenuation plaque (35±32 HU) and ring like attenuation. Especially, ring like attenuation in the TCFA group was 11-fold higher than the non-TCFA group. However, it remains unclear whether this appearance could indicate the presence of deep micro calcification, intraplaque hemorrhage accompanying that affect instability and expansion of plaque. Relationship between plaque shape of plaque core accompanying low CT attenuation and high CT attenuation surrounding it and vulnerable plaque is reported as Napkin-ring sign by other authors (Fig. 1). Specially, it is supposed that Napkin-ring sign reflects large necrotic core that is a characteristics of vulnerable plaque. It is reported that specificity to vulnerable plaque is high, however, relatively, sensitivity is low in histopathological study.

It is supposed that development of vasa vasorum in plaque and intraplaque hemorrhage accompanying that affect instability and expansion of plaque. However, there is no noninvasive im-

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**Fig. 1** Cross sections of a coronary atherosclerotic plaque with napkin-ring sign. The napkin-ring sign can be defined as the presence of two features: a central area of low CT attenuation that is apparently in contact with the lumen; and a ring-like higher attenuation plaque tissue surrounding this central area.

A: Non-contrast enhanced cross sectional CT.

B: Contrast enhanced cross sectional CT.

C: Histopathology reveals a thin-cap fibroatheroma and large necrotic core. Necrotic core correlates with the low CT attenuation and fibrous area correlates with the ring-like higher CT attenuation.

CT: computed tomography

aging to evaluate them. We took an image of CCTA again three minute after routine CCTA imaging and evaluated delayed plaque enhancement. Change ratio of CT value in plaque was obtained. Plaque with characteristics of vulnerable plaque (positive remodeling: remodeling index $>1.1$, low attenuation plaque: CT $<30$ HU) has significantly low change ratio. It was suggested that vasa vasorum might be developed.\(^{22}\)

On the other hand, according to the report of invasive coronary angiography, most of vulnerable plaque has no significant stenosis.\(^{23-28}\) So, evaluation of plaque characteristics gathered attention. However, relationship between stenosis level and vulnerable plaque also has been recognized.\(^{7, 29, 30}\) In the previous report that culprit lesion is not significant stenosis, there was long term between lesion evaluation period and ACS onset.\(^{23-28}\) In the discussion immediately before AMI onset, there are many significant stenosis lesions even if effect of thrombus is excluded.\(^{31-35}\) In COURAGE trial, it is reported that only one predictor of ACS onset from residual stenosis was stenosis level $>50\%$.\(^{36}\) As shown above, vulnerable plaque has higher risk when stenosis level is higher. At the same time, it progresses relatively rapidly while repeating rupture and healing.\(^{37, 38}\) In stenosis level in invasive coronary angiography, effect of positive remodeling is not considered.\(^{39, 40}\) In other words, in a large amount of plaque, even if stenosis level in cross sectional area is significant using pathological sample as standard, if luminal diameter is maintained, it is probable that stenosis level is mild stenosis in invasive coronary angiography.\(^{41}\) From these point of view, CCTA is useful to evaluate vulnerable plaque because CCTA can evaluate positive remodeling, plaque volume and stenosis level in cross sectional area noninvasively. Recently, in comparison with IVUS and VH-IVUS, usefulness of a method to analyze plaque quantification in an automated manner has been recognized.\(^{42-44}\) In meta analysis of 42 studies comparing CCTA and IVUS, sensitivity and specificity were 93% and 92% respectively. Area under curve in receiver-operating curve was 0.97.\(^{45}\) Further, relationship between plaque volume and cardiovascular event observed by CCTA has been reported.\(^{46, 47}\)

III. Prognostic Value of plaque evaluation by CCTA

Clinicians are most interested in whether vulnerable plaque evaluation in CCTA can be a predictor of future cardiovascular events. There are several reports about this.

Motoyama, et al. established 2 feature positive plaque (2FPP) satisfying positive modeling (remodeling index $>1.1$) and low attenuation plaque (CT number $<30$ HU) and 1 feature positive plaque (1FPP) satisfying either one of the conditions in CCTA. They followed up prognosis for two years. As a result, 10 cases (22.2%) of acute coronary syndromes (ACS) occurred from 45 cases of 2FPP and 1 case (3.7%) of ACS occurred from 27 cases of 1FPP for two years. Only two ACSs (0.5%) occurred from 820 cases that did not have both characteristics (2 feature negative plaque (2FNP)).\(^{48}\) Otsuka, et al. observed 1174 plaques in 12727 segments in 895 patients for one year or more (mean 2.3±0.8 years). They reported that napkin-ring sign is an independent ACS predictor in addition to the characteristics of positive remodeling and low attenuation plaque.\(^{49}\) However, it has been reported that stenosis level of lesion and number of diseased vessels are strong predictor of cardiovascular event of CCTA in the past.\(^{50}\) It has not proven whether plaque evaluation gives incremental prognostic value to conventional predictor such as stenosis level of lesion and number of diseased vessels. Moreover, there is no report that incremental value is given to conventional risk stratification such as FRS in the primary prevention and previous reports did not show the discrimination to primary and secondary prevention for study population. Recently, Yamamoto, et al. reported that existence of positive remodeling and low attenuation plaque in CCTA give additional prognostic information to coronary stenosis.\(^{51}\) It is required to discuss how much plaque evaluation in CCTA has incremental prognostic value for conventional predictors in various study population.

Currently, in Japan, prospective multi-center study regarding evaluation of plaque characteristics in CCTA for prognosis is being performed.\(^{52}\) The results are awaited.

IV. Plaque Evaluation by CCTA for Asymptomatic Patients

It has been recognized that plaque evaluation by CCTA is useful for predicting cardiovascular event. Finally, stratification of risk for effective prevention and treatment is required for asymptomatic patients at the health checkup level by CCTA noninvasively. Indication of CCTA has been widened by reduction of radiation exposure and contrast agent due to development of CT devices.\(^{53-58}\) Current guideline does not recommend CCTA for asymptomatic patients even if they are in high risk group.\(^{59}\) Actually, it is reported that evaluation by CCTA in asymptomatic patients provides no incremental prognostic value for coronary calcium score.\(^{60}\) However, there are reports that evaluation by CCTA provides incremental prognostic value for moderately high calcium score or diabetes asymptomatic patients.\(^{61, 62}\) Plaque evaluation in CCTA has not been discussed as incremental prognostic factor for asymptomatic patients. We discussed frequency and the predictor of CT verified vulnerable plaque for 1139 patients who underwent CCTA due to asymptomatic or atypical chest pain.\(^{63}\) CT verified vulnerable plaque was observed in 72 cases (6.3%). Relationship with FRS was low group 0%, intermediate group: 4.3% and high group: 15.5%. It was not necessarily correlated with coronary calcium score (Fig. 2).
diabetes + high risk group was male, diabetes and current smoking. In the future, it is required to discuss how much incremental prognostic value exists in plaque evaluation in which kind of population of asymptomatic patients. Specially, it is important to evaluate incremental prognostic value to coronary calcium score whose usefulness is recognized in risk stratification in asymptomatic patients.

V. Problem in Plaque Evaluation by CCTA

The largest problem in plaque evaluation by CCTA is poor objectivity. Currently, necrotic core area, fibrous area, and calcification in plaque are evaluated by absolute CT number. It is reported that CT value is affected by contrast agent concentration in coronary artery lumen, stenosis level of coronary artery lesion, tube voltage and so on. According to result of meta analysis for 36 papers regarding plaque characteristics analysis by CT number, there are wide variations between lipid-rich and fibrous plaque. It has too many problem to be used in clinical field. It is considered that it is only usable in local clinical setting. Additionally, it is said that interplatform reproducibility is poor in automated coronary quantification software tool.

There is a report that plaque characteristics analysis is adjusted absolute CT number by contrast attenuation and it has usefulness. In order to solve this problem, we developed a new method (labeling method) to analyze plaque tissue characteristics by using not only absolute CT number but also clustering analyzing method adding the three-dimensional distribution, continuity and noise. In computer simulated phantom experiment using this method, effects from factors such as contrast concentration in coronary artery, calcification, and CT value and size of low density region in plaque are resolved. High accuracy analysis results were obtained. No effect by image noise was also observed. After that, we compared necrotic core area and fibrous area in this method with those in VH-IVUS, and more favorable correlation was observed than conventional method using only absolute CT number (Fig. 3).

Pathologically, it is said that about 30–40% of ACS is caused by mechanism other than rupture. It is reported that rupture was observed in 44% of ACS culprit lesion in the study using OCT. However, at present time, it is difficult to predict vulnerable plaque that develops by the mechanism of erosion or calcified nodule by CCTA. Actually, Ozaki, et al. reported that there was no significant difference for plaque characteristics in CCTA between culprit lesion of stable angina and ACS caused by no rupture observed on OCT.

VI. Future Perspective of Plaque Evaluation by CCTA

Recently, fractional flow reserve (FFR) is becoming a standard for indication of revascularization and ischemia evaluation of coronary artery disease. The relationship between vulnerable plaque and stenosis level, and effect of ischemia on plaque destabilization were reported. Recently, FFR-CT that calculates FFR by CCTA imaging has been developed. The usefulness is proven by multi-center study. It is said that
haemodynamic factor such as endothelial shear stress is required for development of arteriosclerosis. Generally, it is said that low shear stress affects plaque development. On the other hand, high shear stress also affects thrombus formation, plaque rupture and instability of plaque characteristics. It is probable that shear stress changes accompanying development of plaque. In PREDICTION trial using IVUS, low shear stress was independent predictor for plaque development after one year. Recently, it is reported that endothelial shear stress can be evaluated by CCTA. Plaque may be assessed by adding physiological information such as FFR and shear stress more comprehensively. As the result, plaque vulnerability could be evaluated more accurately.

Inflammation has a crucial role in instability of plaque. Except fibrous cap thickness, level of macrophage inflammation is most useful for discrimination of vulnerable plaque. However, there is no established noninvasive imaging for plaque inflammation in clinical field. Hyafil, et al. showed that CT contrast agent, composed of iodinated nanoparticles dispersed with surfactant given intravenously to rabbits accumulates in macrophage within atherosclerotic plaque 2 h after injection, allowing for identification of macrophage cells with CCTA. Usefulness of CT imaging using gold-labeled HDL nanoparticle targeting at activated macrophage is also reported. Although molecular imaging by CCTA is useful for vulnerable plaque evaluation, it has not been applied in clinical field.

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Fig. 3 Plaque morphology analysis by conventional CT color map, the labeling method and by VH-IVUS.
A: Curved multiplanar reformatted image of the left main coronary artery demonstrating >75% stenosis.
B: Conventional catheter angiography of the left main coronary artery confirming >75% stenosis.
C: CCTA image orthogonal to the long axis of the left main coronary artery where the lumen diameter was minimal and plaque analysis was performed.
D: CT color map analyses.
E: Labeling method analyses.
F: VH-IVUS analyses.

Low-density peripheral fatty tissue influences necrotic core area (red) quantification by CT-number based measurement; the necrotic core area identified by the labeling method is more consistent with VH-IVUS-derived necrotic core area (red).

CCTA: coronary computed tomography angiography, VH-IVUS: virtual histology intravascular ultrasound
VII. Conclusions

CCTA is the only modality for evaluating coronary artery plaque noninvasively. Currently, prognostic value of plaque evaluation by CCTA is being proven. Indication will be widened by the reduction of radiation exposure and contrast agent volume through development of devices. However, in plaque evaluation, whether incremental prognostic value exists in what kind of population compared to conventional predictor have not been resolved. In the future, quantitative and objective evaluation should be established. Moreover, multi-center large-scale clinical trial would be needed for construct evidence. Vulnerable plaque in CCTA could be diagnosed more correctly by comprehensive assessment and the new technology such as molecular imaging.

Disclosure Statement

None.

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