Identification of Vulnerable Plaques

Various imaging methods allow evaluation in vivo.

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Vulnerable plaques are defined as nonobstructive atherosclerotic lesions that are prone to rupture, causing arterial thrombosis and leading to, for example, acute coronary syndromes (ACS) and stroke.[1,2] A deep understanding of the pathophysiology of vulnerable plaque could play a key role in optimizing the prevention and treatment of arterial thrombosis, potentially reducing its morbidity and mortality. We discuss the recent advances in noninvasive and intravascular imaging that have significantly improved the ability to evaluate vulnerable plaque in vivo.[3,4]

HISTOPATHOLOGY

Thin-cap fibroatheroma (TCFA) is defined as a lipid plaque with a fibrous cap that is < 65 µm thick and is heavily infiltrated by inflammatory cells and macrophages, indicating the important role of inflammation on plaque instability. Furthermore, neovascularization of the arterial wall caused by the proliferation of adventitial vasa vasorum may connect to intraplaque hemorrhage, which is a common feature of advanced lesions, with plaque rupture and luminal thrombi.[5] It is widely recognized that TCFA rupture with subsequent thrombosis is the most common cause of ACS or sudden cardiac death.[6]

The second most common cause is plaque erosion, a significant substrate for coronary thrombosis, followed by calcified nodule, a less frequent entity.[7] Plaque erosion is identified when serial arterial segment with thrombus fails to reveal fibrous cap rupture; typically, the endothelium is absent at the erosion site. *Calcified nodule* refers to a protruding eruptive dense calcified plaque with fibrous cap disruption and thrombi.[8] Although pathology studies were instrumental for a broad comprehension of vulnerable plaque, the potential selection bias and the analysis of a "single snapshot" rather than having prospective longitudinal assessments largely limited the refinement of our knowledge in this setting. Noninvasive and intravascular imaging could potentially overcome these limitations.

CT ANGIOGRAPHY

CT angiography has been well established for evaluating coronary artery stenosis.[9] It also enables the assessment of plaque characteristics, which are categorized as positive remodeling, low attenuation plaques, and spotty calcification in patients with ACS.[10,11] The ring-like enhancement, another feature potentially associated with plaque rupture, has been defined as a low attenuation region with adjacent circumferential thin enhancement in a previous report by Tanaka et al.[12] A subsequent study showed that the frequency of ring-like enhancement was higher in the TCFA group than in the non-TCFA group in images obtained by optical coherence tomography (OCT).[13] Although CT angiography enables the evaluation of the entire coronary system in a noninvasive fashion, some limitations, such as its reduced spatial resolution compared with intravascular imaging modalities, should be taken into account.

MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging (MRI) is capable of detecting features of vulnerable plaque noninvasively, such as intraplaque hemorrhage, a component of the American Heart Association's definition of type VI plaque.[14] This feature is observed as a high signal of T1-weighted imaging and has been associated with strokes of carotid origin.[15,16] MRI can detect coronary artery plaques, as well.[17,18] A recent study showed that the presence of coronary high-intensity plaques obtained by T1-weighted imaging was significantly associated with adverse coronary events.[19] However, coronary plaque imaging using MRI has been challenging due to reduced vessel size compared with the carotids, as well as cardiac and respiratory motion.[20]

INTRAVASCULAR ULTRASOUND

Intravascular ultrasound (IVUS) delivers 100-µm axial resolution images of the arterial wall. IVUS features that are associated with plaque vulnerability include the presence of an echolucent zone, calcium deposits, and positive remodeling.[21,22] Yamagishi et al demonstrated that coronary sites with an acute occlusion have more echolucent zones compared with sites without acute events.[22] Spotty calcium deposition is frequently observed in patients with acute myocardial infarction. Ehara et al demonstrated that the average number of calcium deposits within an arc of < 90° per patient was significantly higher in acute myocardial infarction than stable angina pectoris (SAP), and calcium deposits were significantly longer in SAP patients.[23] Spotty calcifications, especially those that are deep, are frequently observed in lesions with ruptured plaque compared with lesions without ruptured plaque.[24] Although positive remodeling was initially regarded as a protective process in reducing effective luminal narrowing, it has been associated with ACS.[25] Prospective IVUS studies correlating vulnerable plaque features observed on IVUS with adverse cardiovascular events are warranted.

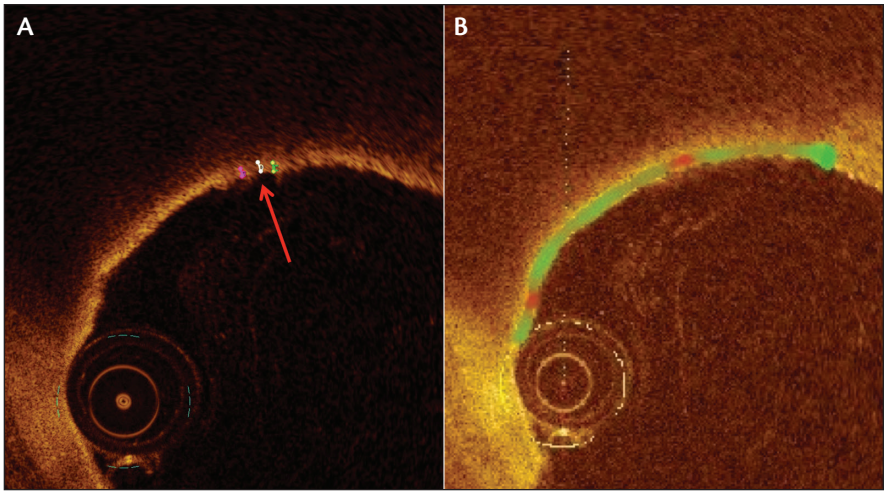

Figure 1. A fibrous cap is identified as a signal-rich homogenous lesion overlying lipid plaque. The current methodology for determining fibrous cap thickness is based on manual individual measurements of arbitrary points (A). A semiautomated method of measuring fibrous cap thickness allows comprehensive quantification of fibrous cap thickness and circumferential distribution (B).

VIRTUAL HISTOLOGY IVUS

Virtual histology (VH) IVUS data are collected with a 20-MHz, 2.9-F phased-array transducer catheter that acquires ECG-gated IVUS data. Briefly, VH-IVUS uses spectral analysis of IVUS radiofrequency data to construct color-coded tissue maps that label plaque into four major components. The initial experience with VH-IVUS has shown good sensitivity, specificity, and predictive accuracy ranging from 80% to 92% in identifying the four plaque components (fibrous, fibrolipid, necrotic core, and dense calcium) compared with histology.[26] TCFA identified by VH-IVUS was more prevalent in those with ACS than in stable angina patients.[27]

Recent longitudinal studies demonstrated that in patients mostly with stable angina, the majority of the TCFAs observed at baseline had healed at 12-month follow-up, whereas untreated nonculprit lesions in patients with ST-elevation myocardial infarction (STEMI) frequently exhibited TCFA morphology that does not change over a 13-month follow-up course.[28,29] The PROSPECT study demonstrated that nonculprit lesions associated with recurrent ischemic events were more likely to be characterized by a plaque burden ≥ 70% or a minimal luminal area ≤ 4 mm^2, or to be classified on the basis of VH-IVUS as TCFA.[30] This was the first trial that investigated the natural history of vulnerable plaque using IVUS. Despite the definition of TCFA derived from VH-IVUS used in the PROSPECT trial, it is important to highlight that this imaging modality does not have the ability to accurately measure the thickness of the fibrous cap due to its insufficient axial resolution. Recently, the correlation between necrotic core size determined by VH-IVUS and histopathology has been questioned; therefore, further validation studies are required to completely elucidate the accuracy of VH-IVUS in detecting vulnerable plaque.[31]

NEAR-INFRARED SPECTROSCOPY

The catheter-based near-infrared spectroscopy (NIRS) has the potential to identify and quantify lipid core plaques, as it can penetrate blood and several millimeters into the tissue. Lipid core plaques are defined as fibroatheroma > 60° in circumferential extent, > 200 µm thick, with a mean fibrous cap thickness < 450 µm.[32,33] Thus, NIRS can detect lipid core plaques in a map with pullback position and degrees of circumferential extent; however, it is unable to indicate the depth of lipid core plaques. The current NIRS system is combined with IVUS

as a single catheter. In a study using histopathology as the gold standard, NIRS was able to identify lipid-rich plaques more accurately than IVUS. Importantly, the combination of NIRS and IVUS was more accurate than both methods individually.[34] Lipid core burden index, one of the output values from NIRS that indicates the amount of lipid in a scanned artery, and its combination with remodeling index calculated by IVUS were correlated with OCT findings of lipid plaque and TCFA.[35,36] Clinically, NIRS-IVUS might predict the occurrence of periprocedural myocardial infarction during percutaneous coronary intervention by identifying extensive lipid core plaques, most likely due to embolization of plaque contents.[37]

In addition, Oemrawsingh et al suggested in a single-center, prospective, observational study that coronary lipid core burden index obtained by NIRS in nonculprit coronary arteries in patients with SAP and ACS has the potential to be associated with major adverse cardiac events during 1-year follow-up.[38] Additional investigation is required, however, to clarify whether NIRS findings can play a role in the identification of vulnerable plaque.

OCT

Intravascular OCT is a near-infrared light-based imaging system that delivers images with 10- to 20-µm axial resolution. It therefore enables visualization of blood vessel wall microstructures in vivo at an unprecedented level of detail.[39]

TCFA

OCT is the only imaging modality available for clinical use that is capable of measuring the fibrous cap thickness overlying a lipid plaque, therefore enabling the detection of TCFA. Kume et al demonstrated that after accounting for tissue shrinkage during histologic preparation, there is a good correlation between OCT and histologic examination in determining fibrous cap thickness ($r = 0.9$; $P < .001$).[40] Importantly, fibrous cap thickness varies according to the clinical presentation, as shown by in vivo studies using OCT measurements. Patients with STEMI were found to have a considerably thinner fibrous cap in comparison with patients with non-STEMI and stable angina.[41] Takarada et al demonstrated that statin therapy significantly increased the fibrous cap thickness in patients with hypercholesterolemia at 9-month follow-up.[42] Furthermore, ruptured TCFA observed in the carotids has been demonstrated as a predictor of transient ischemic attack or stroke.[43] Recent OCT study showed that atorvastatin therapy at 20 mg compared with 5 mg provided a greater increase in fibrous cap thickness in coronary plaques of patients with unstable angina pectoris.[44] However, the current methodology for determining fibrous cap thickness is based on manual individual measurements of arbitrary points (ie, the thinnest regions determined by visual assessment), which might cause high variability and reduced accuracy (Figure 1). Besides, such one-dimensional analysis of fibrous cap thickness does not take into account the three-dimensional (3D) morphology of coronary artery disease, which largely limited the advancement of the clinical knowledge in this field.

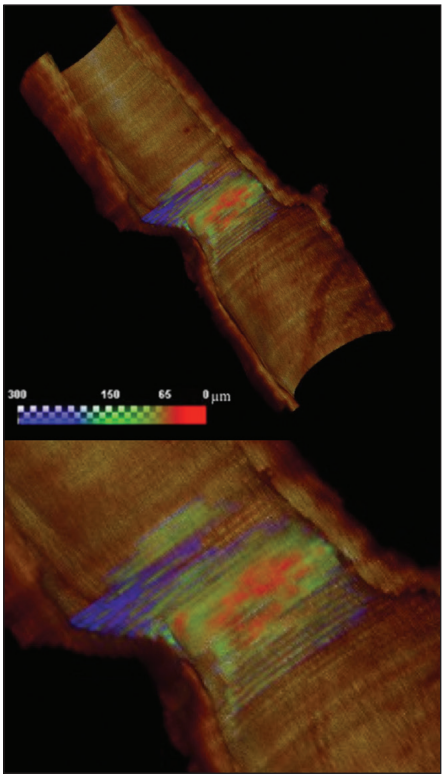

Figure 2. Three-dimensional visualization of longitudinal and circumferential distribution of fibrous cap. A representative case of segmented fibrous cap in 3D rendering with a continuous color map, from blue (fibrous cap > 150 µm) to green (fibrous cap, 65–150 µm) to red (fibrous cap < 65 µm).

Aiming at overcoming this important limitation of previous studies, a semiautomated method that allows comprehensive quantification of fibrous cap thickness and 3D visualization of its longitudinal and circumferential distribution along the vessel has been investigated (Figure 2). The method has been found to be highly accurate, yet more consistent than human experts.[45,46] Moreover, Galon et al demonstrated that the novel OCT-based 3D quantification of the fibrous cap showed thinner fibrous cap thickness and larger areas of TCFA in nonculprit sites of STEMI compared with stable angina.[47] Although the mechanisms of fibrous cap rupture remain unclear, it is possible that its mechanical stability may not only depend on a focal, thin point, but rather on the thickness of confluent regions of thin cap distributed along the plaque. Therefore, we need to further investigate in a prospective fashion whether this more comprehensive methodology to identify and quantify different fibrous cap thicknesses along the

plaque may refine our ability to predict future plaque rupture and its devastating consequences.

Macrophages

Macrophage infiltration in the fibrous cap plays an important role in the pathogenesis of plaque rupture.[3] OCT is the only imaging modality that can visualize macrophages in vivo (Figure 3). Terney et al demonstrated good correlation between OCT and histologic measurements of fibrous cap macrophage density.[48] Tahara et al demonstrated in murine aortas that OCT shows excellent correlation with histology in macrophage identification.[49] Recently, Di Vito et al demonstrated that OCT was able to identify and quantify macrophage presence in coronary artery specimens using tissue property indexes (sensitivity of 100% and specificity of 96.8%).[50] Although the identification of fibrous cap inflammation in vivo by OCT still lacks correlation with clinical outcomes, Galon et al demonstrated more inflammation in the fibrous cap of nonculprit lesions of STEMI compared with stable angina patients.[47]

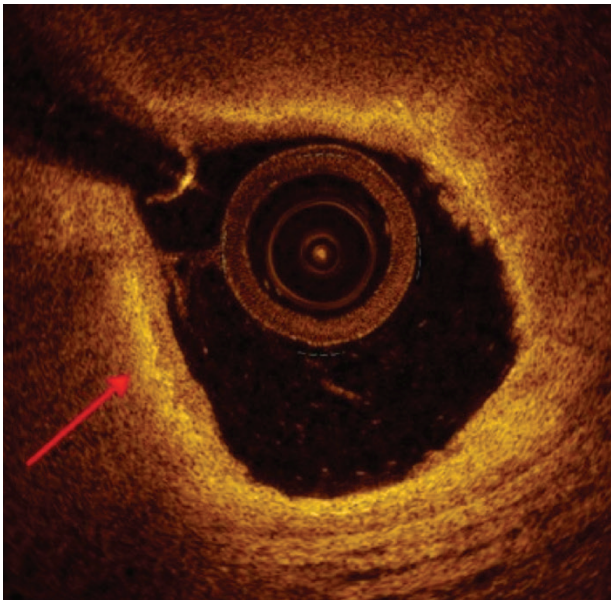

Figure 3. Macrophages are identified as signal-rich, confluent, or punctuate lesions (red arrow).

Neovascularization

Neovascularization is a common feature of vulnerable plaque. The high resolution of OCT enables the detection of neovascularization in vivo. Kitabata et al showed that the high-sensitivity C-reactive protein levels in the neovascularization group were significantly greater than those in the non-neovascular group.[51] Tian et al showed that in patients with ACS, culprit plaques with neovascularization had vulnerable features such as thinner fibrous cap, greater lipid arc, longer lipid core length, and more frequent TCFA compared with those without neovascularization.[52] Kato et al demonstrated that neovascularization was more frequently located close to the lumen in patients with ACS compared with non-ACS.[53]

Erosion and Calcified Nodules

OCT has the ability to distinguish the etiology of coronary thrombosis. OCT-derived erosion is defined as the absence of fibrous cap disruption and the presence of thrombus. Calcified nodule is defined as fibrous cap disruption detected over a protruding, superficial calcified plaque. Jia et al demonstrated in patients with ACS that 31% of the lesions were classified as erosion and 8% as calcified nodules.[54] Furthermore, calcified nodules were also observed by OCT in unstable carotid plaques.[43] However, OCT has some limitations to distinguish the etiology of acute coronary thrombosis. First, the definitions of plaque erosion and calcified nodule as detected by OCT were not validated by pathology. Second, the presence of (red) thrombus overlying the culprit lesion might preclude the ability to estimate plaque characteristics. Finally, OCT does not have sufficient resolution to detect a single layer of endothelium; therefore, the pathologic definition of plaque erosion cannot be directly applied to OCT.

CONCLUSION

Although several imaging modalities have been investigated for the detection of morphologic aspects of vulnerable plaque in vivo with promising results, a precise prediction of which plaques will cause future adverse events is still lacking. Although OCT seems to be the most suitable imaging system in this setting due to its high resolution and unique ability to measure fibrous cap thickness, neovascularization, and inflammation, potential methodologic limitations observed in the majority of the studies that utilized OCT as reference might have precluded a better understanding of this complex scenario. A recent methodology that accounts for the 3D nature of atherosclerosis distribution might shed light on this topic in future prospective studies. ■

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