Intracoronary Imaging for Detecting Vulnerable Plaque

Kenichi Fujii, MD; Hiroyuki Hao, MD; Mitsumasa Ohyanagi, MD; Tohru Masuyama, MD

It is now generally recognized that acute coronary syndromes most commonly result from disruption of thin-cap fibroatheroma (TCFA), which is characterized by a large necrotic core with an overlying thin-fibrous cap measuring <65μm. Recent advances in intracoronary imaging modalities have significantly improved the ability to detect TCFA in vivo. Intravascular ultrasound (IVUS) is perhaps the most promising modality that has been used more than 15 years to evaluate atherosclerotic plaque. IVUS has revealed a lot of the clinical evidence regarding vulnerable plaque detection in live humans. Recently, by analyzing the IVUS acoustic signal before demodulation and scan conversion, IVUS radiofrequency analysis can be used to differentiate adjacent smaller areas of atherosclerotic plaque with heterogeneous composition. Coronary angioscopy allows direct visualization of the coronary artery wall and provides detailed information of the luminal surface of plaque, such as color, thrombus or disruption. Optical coherence tomography imaging, recently been introduced for in vivo human imaging, offers a higher resolution than any other available imaging modality, and can visualize a thin fibrous cap measuring <65μm. In this review, we will discuss the features and limitations of each imaging modalities for detecting TCFA. (Circ J 2013; 77: 588–595)

Key Words: Coronary angioscopy; Intravascular ultrasound; Optical coherence tomography; Vulnerable plaque

Management of coronary artery disease (CAD) has 2 goals: to reduce ischemia and symptoms, and to prevent acute coronary syndrome (ACS) and death. These are controlled by different mechanisms: symptoms and ischemia, by the reduced oxygen supply/demand ratio (usually because of coronary atherosclerosis), and ACS and death, usually by disruption of vulnerable plaques.

Medical management is pivotal in all patients with CAD. The first step is to identify and treat any associated diseases that can precipitate angina by increasing myocardial oxygen demand (eg, tachycardia and hypertension) or by decreasing the amount of oxygen delivered to the myocardium (eg, heart failure, pulmonary disease, or anemia). The second step is to manage CAD risk factors (eg, smoking cessation, blood pressure control, and lipid and diabetes management), as well as to prevent myocardial infarction with lifestyle changes and pharmacological treatment.

It is now widely recognized that plaque rupture with subsequent thrombus formation is the most frequent cause of ACS.1 It has been postulated that thin-cap fibroatheromas (TCFA), which are characterized by a large necrotic core with an overlying thin fibrous cap measuring <65μm, are the precursor of plaque rupture.2 A greater understanding of the mechanisms of vulnerable plaque formation is necessary for advancement in the diagnosis, treatment, and prevention of ACS. A good animal model would help us to understand not only how plaque progresses and thrombus formation occurs, but also how to take measures to prevent ACS events. However, the lack of a suitable animal model for vulnerable plaque has considerably hampered progress in the research into understanding this field. Therefore, significant advances in our understanding and natural history of plaque formation and progression can only be achieved by improving our ability to accurately identify and locate these lesions in the clinical setting. Detection based on morphology alone has been proposed using intracoronary imaging modalities such as intravascular ultrasound (IVUS), optical coherence tomography (OCT), and coronary angioscopy (CAS). In this review, we provide a short description of their techniques, validations, clinical utility, and limitations for detecting vulnerable plaques, especially those that are prone to rupture.

IVUS

IVUS is a catheter-based imaging modality that provides high-resolution cross-sectional images of the coronary arterial walls. High-frequency (20–40MHz) IVUS is capable of visualizing the 3 layers of the muscular arterial wall, such as that of the coronary arteries. In normal adult human arteries, the inner bright acoustic reflection layer is derived from the interface of blood with the intima and internal elastic lamina and the second bright interface (third layer) is from the external elastic lamina and adventitia, and the middle echolucent zone reflects the media.3 Therefore, grayscale IVUS allows qualitative measurements of luminal and vessel areas in vivo. Observation of focal arterial enlargement at the site of

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Cardiovascular Division (K.F., T.M.), Department of Surgical Pathology (H.H.), and Division of Coronary Heart Disease (M.O.), Hyogo College of Medicine, Nishinomiya, Japan
Grant: none.
Mailing address: Kenichi Fujii, MD, Hyogo College of Medicine, Cardiovascular Division, 1-1 Mukogawa-cho, Nishinomiya 663-8501, Japan. E-mail: kfujii@hyo-med.ac.jp
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Coronary plaque has led to the theory of arterial remodeling in response to plaque development. Histological study has demonstrated a significant positive correlation between internal elastic lamina area and plaque area in a necropsy study of 136 human coronary arteries. Liminal area is unaffected by plaque growth until the lesion reached 40% area stenosis; >40% area stenosis, the luminal area is diminished in a close relationship with the percentage of stenosis (positive remodeling). Although initially thought of as a protective process in reducing effective luminal narrowing, positive remodeling has been associated with ACS and angiographically complex lesions. The pathophysiological mechanisms associated with arterial remodeling and plaque vulnerability have not been fully elucidated. However, inflammation may represent a common link. Inflammatory markers such as macrophages and matrix-metalloproteinases have an established role in the pathophysiology of plaque rupture. Histopathologic study has demonstrated an association between histologic markers associated with plaque inflammation and positive remodeling in femoral arteries. Although there is not a prospective IVUS study demonstrating that lesions with positive remodeling correlate with future thrombotic events, assessment of coronary arterial remodeling may be important for identifying vulnerable plaques.

The effect of calcium on plaque vulnerability remains unclear. An IVUS study reported that there is a significant difference in the pattern of coronary calcium deposition at the target lesion, particularly with respect to size and number of the deposits, among patients with acute myocardial infarction (AMI), unstable angina pectoris (UAP), and stable angina pectoris (SAP). “Spotty calcium” deposition is frequently observed in patients with AMI; in that study, the average number of calcium deposits within an arc <90° in AMI patients was significantly higher than in SAP patients (AMI 1.4±1.3, UAP 1.0±1.1, SAP 0.5±0.8, P<0.0005), and the average age length of each calcium deposit in patients with AMI and UAP was significantly smaller than in SAP (AMI 2.2±1.6, UAP 1.9±1.8, SAP 4.3±3.2 mm, P=0.0001). In accordance with that IVUS study, we have reported that spotty calcification, especially deep calcium deposits, is frequently observed in lesions with ruptured plaque compared with lesions without ruptured plaque. Although previous pathological study demonstrated that inflammation and calcification are the primary determinants of plaque rupture, the precise histopathologic mechanism of spotty calcium deposition in vulnerable plaques has not been fully elucidated. However, spotty, deep calcium deposits could be a surrogate marker for plaque vulnerability.

Plaque morphology by ultrasound is often characterized by the intensity of the signals as soft echoes (hypoechoic), very high-intensity reflectors that create distal shadowing, and echoes of intermediate intensity (high echoic), features that correspond to tissue, calcium, and fibrosis, respectively. Echolucent or signal-free zones have been found to represent lipidic tissue accumulation. In addition, recent several IVUS studies have demonstrated that atherosclerotic plaque with ultrasound attenuation without dense calcium is related to the no-reflow phenomenon and as a result larger infarct size and higher incidence of adverse event following PCI in patients with ACS. In line with those studies, we have reported that plaque with ultrasound attenuation without dense calcium evaluated by IVUS is associated with the absence of ST-segment resolution after PCI in patients with AMI. In a previous report of human cadaver coronary arteries, plaque with ultrasound attenuation contained fibrolipidic tissue and necrotic core. Another histopathologic study suggested that ultrasound attenuation evaluated by IVUS was associated with microcalcification and lipidic tissue containing scattered cholesterol clefts causing ultrasonic wave reflection and dispersion. In addition, authors of a previous animal study reported that white thrombus contained densely homogenous cellular elements and produced an attenuated ultrasound pattern.

Other IVUS features associated with plaque vulnerability may include eccentric pattern, presence of an echolucent zone, and of thrombi. In addition, IVUS can clearly visualize ruptured plaque. Although our goal is to identify vulnerable plaques before, not after, they rupture, assessment of ruptured plaques provides a lot of information regarding plaque vulnerability. A 3-vessel IVUS study showed that at least 1 plaque rupture was found somewhere other than at the culprit lesion in patients with ACS. Another 3-vessel IVUS study reported that plaque ruptures occurred mainly in proximal segments of the left anterior descending artery, the proximal and distal segments of the right coronary artery, and the entire left circumflex artery.

The major limitation of IVUS is its insufficient spatial resolution. IVUS, at frequencies in the 20–40-MHz range, has an axial resolution of 100–200μm and a lateral resolution of 250μm. Although it can visualize deep structures, IVUS is not a suitable imaging modality for detecting the very thin fibrous cap that is 1 of the main components of vulnerable plaques. It is necessary to increase the imaging frequency of IVUS to improve spatial resolution. However, increased imaging frequency also leads to reduced contrast between blood and non-blood tissue that, in turn, makes difficult the segmentation of the blood-filled lumen from plaque. In the near future, 60-MHz IVUS images may resolve this issue and appear to enable improved detection of rupture-prone plaque in the clinical setting.

Second, grayscale IVUS may not accurately assess plaque composition, because atherosclerotic plaque can have a complex and heterogeneous composition consisting of a mixture of plaque components, such as lipids, fibrotic tissue, calcified nodules and extracellular matrix.

These issues preclude IVUS from becoming an absolute intracoronary imaging modality in the assessment of plaque vulnerability.

**IVUS Radiofrequency Analysis**

Grayscale IVUS images are unsuitable for accurately differentiating adjacent smaller areas with heterogeneous composition, because they indicate the overall composition of large homogeneous regions, such as a predominantly lipidic area. Coronary atherosclerotic plaques are heterogeneous in most cases. In addition, previous histopathologic study has demonstrated that the necrotic core within a plaque, which is an important component of vulnerable plaques, has adjacent areas of microcalcification. These limitations have been partially overcome by analysis of the IVUS acoustic signal before demodulation and scan conversion. At present, 3 modalities are clinically used: virtual histology IVUS (VH-IVUS, Volcano Therapeutics, Rancho Cordova, CA, USA), iMAP-IVUS (Boston Scientific, Santa Clara, CA, USA), and integrated backscatter IVUS (IB-IVUS, YD, Nara, Japan).

The first commercial available US radiofrequency signal-based tissue morphological analysis modality was VH-IVUS software. IVUS radiofrequency signal data for the regions of interest (ROI) are processed by calculating a mathematical autoregressive model for each line in a ROI and then averaged over the width of the ROI. The tissue characterization with this system is based on 7 spectral parameters (intercept, slope,
mid-band fit, and minimum and maximum powers and their corresponding frequencies) extracted from calibrated tissue spectra.\textsuperscript{30} VH-IVUS data are collected with a 20-MHz, 2.9F phased-array transducer catheter (Eagle Eye\textsuperscript{TM} Gold, Volcano Therapeutics) that acquires IVUS data that are ECG-gated. Compared with histologic specimens of human coronary arteries, VH-IVUS has a sensitivity, specificity, and predictive accuracy ranging from 80\% to 92\% in identifying the 4 plaque components: fibrous, fibro-lipid, necrotic core, and dense calcium. The predictive accuracy of VH-IVUS to identify the 4 plaque characteristics ranges from 87\% to 97\% compared with directional coronary atherectomy specimens.\textsuperscript{32} Therefore, VH-IVUS may be useful in differentiating the adjacent smaller areas with heterogeneous composition of atherosclerotic plaque. Previous clinical study demonstrated that VH-IVUS derived TCFA was more frequently observed in ACS patients than in SAP patients.\textsuperscript{33} Moreover, a recent trial,\textsuperscript{34} Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT), studied 700 patients with ACS using 3-vessel grayscale IVUS and VH-IVUS to quantify the clinical event rate because of atherosclerotic progression and to identify those lesions that place patients at risk for unexpected adverse cardiovascular events (sudden death, cardiac arrest, heart attacks and unstable or progressive angina). The highest risk plaque type was VH-derived TCFA with a minimum luminal area ≤4 mm\textsuperscript{2} and a plaque burden ≥70\%. This was the first prospective trial to provide a natural history study of vulnerable atherosclerotic plaque using VH-IVUS. However, the major limitation of this trial was that the most clinical adverse event was UAP rather than AMI or death. Moreover, a histopathologic validation study demonstrated that the necrotic core area is underestimated by the VH-IVUS algorithm.\textsuperscript{35} The main reason for this underestimation is the lack of an intraplaque hemorrhage component in the VH-IVUS algorithm.

Another commercially available system is the iMAP software, which uses a 40-MHz single rotational transducer (Atlantis\textsuperscript{TM} SR Pro, Boston Scientific) to obtain the radiofreQUENCY signal. iMAP uses a pattern recognition algorithm on the spectra that were obtained from fast Fourier transformation and a histology-derived database.\textsuperscript{36} Ex vivo validation demonstrated accuracies at the highest level of confidence: 97\%, 95\%, and 98\% for necrotic, lipidic, fibrotic and calcified regions, respectively.\textsuperscript{37} A previous in vivo study compared the findings of iMAP and VH-IVUS-derived tissue characterization, showing a significant and systematic variability in plaque composition estimates.\textsuperscript{38} Although iMAP may have higher resolution than VH-IVUS because a higher frequency IVUS catheter is used to obtain the radiofrequency data, a prospective natural history study of vulnerable atherosclerotic plaque using iMAP is absent.

IB-IVUS also uses a 40-MHz single rotational transducer (ViewIT, Terumo, Tokyo, Japan), and is an alternative approach to the 2 previous modalities. Fast Fourier transformation extracts frequency components of a signal buried in the original IVUS signal. IB is the average power of the fast Fourier transformation IVUS radiofrequency backscatter signal from tissue. IB values for the various plaque components can then be calculated to construct color-coded IB-IVUS tissue maps.\textsuperscript{39} When compared with the histologic results, the sensitivity of IB-IVUS for calcific, fibrosis, and lipid-rich plaques, has been 90\%, 84\%, and 90\%, respectively.\textsuperscript{40} A previous study followed 160 non-target lesions with moderate stenosis in patients with SAP, and 12 plaques caused ACS after the initial IVUS examination.\textsuperscript{41} Although there was no significant difference in plaque area between the lesions in patients with ACS and non-ACS, the percentage lipid area was significantly greater in the lesions in patients with ACS (72±10\% ACS vs. 50±16\% non-ACS; P<0.0001).

Although each of the 3 modalities of IVUS radiofrequency analysis has advantages in the diagnosis of vulnerable plaques because of the ability to characterize tissue heterogeneity, there are some limitations. The first is the lack of the early or organized thrombus component in the algorithms of these 3 modalities, which may limit recognition of certain vulnerable plaques. Second, when dense calcium is located at the surface of plaque, the characterization of the tissues behind is suspicious because it is hard to obtain accurate radiofrequency data from them. As shown in Figure 1, necrotic core is frequently observed behind dense calcium on these modalities. Finally, histopathologic validation studies are limited and validation work is still required for more precise diagnosis of vulnerable plaque.
Angioscopy

CAS uses projected white light through thin, flexible glass fibers incorporated into catheters in order to see the color of the arterial surface through a clear saline injection, permitting diagnosis of thrombus, and yellow or white plaques. Luminal irregularities, such as plaque rupture, can be also observed. Atherosclerotic plaques usually appear as white or yellow protrusions into the lumen that may be continuous with the normal vessel wall. Histopathologic analysis of atherectomy specimens of coronary lesions from patients has revealed that white-colored plaques are predominantly fibrous and deep-yellow plaques represent atheroma or degenerated fibrous plaque with patchy necrosis. Intimal cholesterol in the arterial wall contains carotenoids, which are yellow-colored and likely give lipid-containing plaques their characteristic yellow color. Platelet-rich thrombus is characterized as white material and fibrin/erythrocyte-rich thrombus as red material protruding into the lumen. Furthermore, yellow plaques are frequently observed at the culprit lesions of ACS. A previous study followed 552 patients who underwent coronary catheterization and angioscopic examination for the diagnosis of CAD and the number of yellow plaques was counted prospectively. Among the patients, ACS events were detected in 39 patients during a follow-up interval of 57.3±22.1 months, and the number of yellow plaques was significantly higher in the patients with an ACS event than in those without (3.1±1.8 vs. 2.2±1.5; P=0.008).

Despite these clinical data, the inability to see through blood because of its opaque nature and the resulting need to remove blood from the visual field remain the primary obstacles to the widespread and routine use of CAS to evaluate plaque morphology. In addition, the presence of superficial calcium also correlates with yellowish plaque on CAS (Figure 2).

OCT

OCT uses near-infrared light and cross-sectional images are generated by measuring the echo time delay and intensity of the light that is reflected or backscattered from the arterial wall. The bandwidths of the infrared light utilized in OCT are far higher than those of US, resulting in greatly increased image resolution. In fact, current OCT provides intravascular images with 15-μm axial resolution, about twice the size of a red blood cell. Because OCT measures the intensity of light returning from within a tissue, tissue having higher heterogeneity of the optical index of refraction show stronger optical scattering and therefore a stronger OCT signal. The intima in the normal arterial wall is normally represented by the bright signal of collagen fibers. The media gives a dark, homogeneous signal because it has less fiber and more smooth muscle cells. The adventitia is also represented by the bright signal of collagen fiber. Therefore, fibrous plaques present as homogeneous, signal-rich regions with low attenuation on OCT because of reflection from the collagen fibers, whereas calcific plaques are characterized by well-delineated, signal-poor regions with sharp borders, and lipid-rich plaques by signal-poor regions with diffuse borders (Figure 3). Previous histopathologic validation studies report that the sensitivity and specificity for detecting fibrous plaques were 71–79% and 98–99%, respectively; for fibrocalcific plaques, 95–96% and 97%, respectively; and for lipid-rich plaques, 90–94% and 90–92%, respectively. Another advantage of OCT is the detection of the thin fibrous cap, which is a major component of vulnerable plaques. Because the fibrous cap is mainly composed of smooth muscle cells and collagen fibers, it normally presents as a high-intensity region with low attenuation on OCT. A preclinical validation study evaluated the feasibility of OCT to measure fibrous cap thickness in lipid-rich plaques from coronary arterial segments of 38 human cadavers using histology as the “gold standard”. Good correlation (r=0.90, P<0.001) and agreement (mean difference, –24±44 μm) were observed between the OCT and histologic measurements, with surprisingly low intraobserver (13±41 μm) and interobserver (20±59 μm) variability. OCT has been studied in vivo in patients with ACS and SAP, and the results describe that plaque characteristics are associated with different clinical presentations. Lipidic plaques and TCFA (defined by lipidic plaque with cap thickness <65 μm) are frequently observed in AMI patients compared with SAP patients, but some TCFA are observed even in patients with SAP. OCT has been also used to show the difference in fibrous cap thickness according to clinical presentation. Patients with ST-elevation AMI show significantly lower median mean values of the minimum thickness of the fibrous cap (47 μm) compared with non-ST-elevation AMI (53.8 μm) and SAP patients (102.6 μm). On the basis of those findings, OCT is the promising imaging modality for visualizing the morphological features of vulnerable plaques. Its major limitations.
On OCT images, lipidic tissue appears as low-signal-intensity regions with diffuse borders because of the strong optical absorption of lipids at light wavelengths around 1,000 nm. Therefore, another tissue could also present as a low-intensity region if it has a similar strength of light absorption at similar wavelengths (eg, thrombus, Figure 4). A previous ex vivo include a complex technique similar to CAS that requires removal of red blood cells from the imaging field, such as with saline or contrast injection, and poor tissue penetration. Thus, the vessel remodeling status, which is a main finding for plaque vulnerability, cannot be evaluated by OCT. Another limitation is related predominantly to the features of near-infrared light.

**Figure 3.** Correlation between optical coherence tomography (OCT) and histologic images of human coronary atherosclerotic plaques obtained at autopsy. (A–C) OCT images of plaque consisting mainly of fibrous tissue, lipidic tissue, and calcific tissue. (D) OCT image of plaque of fibrous tissue (Masson trichrome stain). (E,F) Corresponding histologic images of lipidic and calcific plaques (H&E).

**Figure 4.** Low-signal-intensity plaque. (A) OCT image of plaque with low-signal intensity and diffuse border. Similar image to lipid-rich plaque. (B) Corresponding histologic image from (A) showing replacement by thrombus of vascular smooth muscle cells and collagen fibers. (C) Magnified image of the inset in (A) and (B). There is extensive fibrin within the plaque replaced by collagen fibers (Masson trichrome stain).
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Complicated plaques with surface defects, and/or hematoma-hemorrhage, and/or thrombosis. The initial (type I) stage of human atherosclerosis contains atherogenic lipoprotein from an increase in macrophages and formation of scattered macrophage foam cells. This atherogenic lipoprotein and macrophage foam cells is considered to be “lipid”. In the advanced stage, fibroatheroma is characterized by distinct layers of superficial fibrous tissue surrounding an area of necrotic core, which contains numerous cholesterol clefts and cellular debris (type V). Although the necrotic core is the main component of a vulnerable plaque, it is also characterized as “lipid” on intracoronary imaging. The necrotic core has to be distinguished from other lipids for accurate in vivo diagnosis of vulnerable plaque with imaging modalities. However, there is no large difference in the echogenicity on IVUS, light intensity on OCT, and color grade on CAS between “lipids” at early stage and those at the advanced stage (Figure 5).

Finally, it is still unclear what kind of index is ideal for quantitatively representing plaque vulnerability. It could be the thickness of the fibrous cap, the size of the necrotic core, or the remodeling index. Further natural history studies with large populations are required to ascertain, before an event occurs, which index is definitely ideal.

Conclusion

Although several intracoronary imaging modalities have been developed and are used in the clinical setting, the detection of rupture-prone plaques is still challenging. Most of these modalities have “exciting” features, but none has proven its value in extensive in vivo validation and most lack prospective natural history data. Although use of multiple modalities in the 1 patient is practically and ethically difficult, these various modalities may complement each other. A multiple-modality probe, which will significantly enhance detailed analysis of rupture-prone plaques, is currently under development. Nevertheless, although two-thirds of ACS events result from the rupture of TCFA, the remaining events are caused by erosion of the intimal surface and calcified nodules with subsequent

![Figure 5. Early stage of atherosclerotic plaque formation. (A) Histologic image showing macrophage foam cells accumulating within fibrous tissue. (B) Magnified image of the inset in (A). (C) Corresponding OCT image of (A) showing thin-cap fibroatheroma a low-signal intensity with a diffuse border.](image-url)
thrombus formation. Therefore, we should continue to deepen our understanding of the pathophysiology of vulnerable plaque formation.

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