Invasive Imaging of Vulnerable Atherosclerotic Plaques in Coronary Artery Disease
Shiro Uemura, MD, PhD

Coronary artery disease remains a major cause of morbidity and mortality in many developed countries, despite the multidisciplinary approach to its prevention and treatment. Over the past 2 decades, several catheter-based imaging modalities have been developed for precisely visualizing the morphology of coronary plaques that are susceptible to causing subsequent cardiovascular events. This review article summarizes the pathology of vulnerable plaque as a target for invasive imaging technology, and discusses the current role of invasive coronary imaging technologies in identifying high-risk coronary atherosclerotic lesions and supporting clinical decision-making. (Circ J 2013; 77: 869–875)

Key Words: Imaging; Intravascular ultrasound; Optical coherence tomography; Plaque vulnerability

Coronary artery disease (CAD) is a slowly progressive inflammatory disease of the arterial wall whose clinical manifestation is commonly both serious and sudden in onset after a long latent period.1–4 Despite significant advances in the clinical approach to its prevention and treatment, CAD still remains a major cause of morbidity and mortality in many developed countries.5,6

In patients with acute coronary syndrome (ACS), the coronary artery culprit lesion is usually characterized by advanced atherosclerotic changes with concomitant thrombus formation.7,8 The term “vulnerable plaque” is used to specify a high-risk plaque susceptible to sudden development of an occlusive intraluminal thrombus and subsequent catastrophic cardiovascular events.9–12 Recent studies have shown that vulnerable plaque can develop not only in native coronary arteries but also in the neo-intima after long-term coronary stent implantation.13,14

Over the past 20 years, considerable effort has been made to identify methods of precisely identifying high-risk coronary plaques before their rupture, with the overarching goal of preventing critical coronary events. Two categories of imaging technology, invasive and non-invasive, are currently used to evaluate the vulnerability of coronary atherosclerotic plaques. Catheter-based intravascular imaging technologies have shown particularly strong progress in recent years. Compared with non-invasive technologies, current invasive imaging modalities have advantages in terms of higher spatial resolution, precise plaque localization, and real-time image processing. In this article, I review the pathology of vulnerable plaque as a target for invasive imaging technology, and discuss the current role of invasive coronary imaging technologies in identifying high-risk coronary atherosclerotic lesions, as well as the potential use of these technologies in improving clinical decision-making.

Pathological Background of Vulnerable Plaque in Coronary Arteries

The term “vulnerable plaque” was originally used by Muller et al to define the important factors that trigger the onset of acute cardiovascular disease.15,16 Their hypothesis was that occlusive coronary thrombosis is caused by 3 factors: (1) an atherosclerotic plaque becoming vulnerable to rupture, (2) stress causing the plaque to rupture, and (3) increased coagulability contributing to complete occlusion of the coronary artery lumen. In fact, postmortem pathological studies of the victims of sudden cardiac death have revealed that more than 70% of cases of ACS are attributable to the formation of occlusive thrombus that is preceded by plaque rupture.17,18 However, as noted in those autopsy studies, plaque rupture is not the sole pathological cause of coronary events; no rupture was seen in the remaining 30% of the culprit lesions, which instead showed features such as plaque erosion or calcified nodules. In current clinical practice, these non-rupture-type features of the baseline lesions are also considered to be characteristics of vulnerable coronary plaque (Table 1, Figure 1).

Plaque Rupture

The plaque type most likely to rupture is the thin-cap fibroatheroma (TCFA), which is diagnosed pathologically when the plaque has a large lipid or necrotic core (>40% of total lesion cross-sectional area) and a thin fibrous cap (<65 μm thick).9,19 An autopsy study of ruptured plaques in patients with sudden cardiac death found that 95% of these caps measured <64 μm thick.9 Notably, a recent computer simulation study showed that fibrous cap thickness and necrotic core size are independent determinants of plaque disruption.20 Additionally, TCFA is frequently accompanied by macrophage infiltration and ma-
Matrix metalloproteinase expression in the fibrous cap covering the lipid core. Many studies have pointed out that high macrophage density is characteristic of lesions vulnerable to rupture. Ex vivo studies of human coronary artery plaques have shown that the density and pattern of macrophage infiltration at the plaque shoulders correlate with the degree of vulnerability. Chronic inflammation within TCFA also stimulates smooth muscle cell apoptosis within the fibrous cap, development of calcification, and heat generation. Intraplaque neovascularization is another unique morphological feature of TCFA, usually originating from the adventitial vasa vasorum. Intraplaque microvessels are immature and leaky because they lack a basement membrane and pericytes, and their deterioration is known to cause intraplaque hemorrhage. This phenomena results in both rapid enlargement of the plaque and luminal stenosis.

The abovementioned pathological features of TCFA are candidate targets for coronary artery imaging with the goal of detecting plaque vulnerability. However, it should also be noted that clinically silent plaque rupture is not uncommon.

### Plaque Erosion

Although standard diagnostic criteria have not been defined, plaque erosion is characterized pathologically by a continuous intimal layer without rupture or discontinuation, usually accompanied by an intraluminal thrombus overlying a modestly occlusive plaque. Autopsy studies have shown that 20–40% of acute coronary events are attributable to non-ruptured plaques, indicating that coronary thrombosis resulting from plaque erosions is not rare, but rather an unexpectedly common phenomenon. In current clinical practice, it is difficult to diagnose plaque erosion using imaging technologies, because the pathogenesis of plaque erosion has not been elucidated and no currently available imaging modalities can differentiate the existence of endothelial

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**Table 1. Pathological Targets of Vulnerable Plaque Imaging**

<table>
<thead>
<tr>
<th>Macroscopic pathology</th>
<th>Microscopic pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive vascular remodeling</td>
<td>Thin fibrous cap covering lipid core</td>
</tr>
<tr>
<td>Large necrotic or lipid core</td>
<td>Macrophage infiltration</td>
</tr>
<tr>
<td>Luminal thrombus</td>
<td>Plaque neovascularization</td>
</tr>
<tr>
<td>Plaque hemorrhage</td>
<td>Endothelial denudation</td>
</tr>
<tr>
<td>Spotty calcification</td>
<td>Smooth muscle cell apoptosis</td>
</tr>
<tr>
<td>Protease expression (MMP, etc)</td>
<td>Endothelial adhesion molecule expression (VCAM-1, etc)</td>
</tr>
</tbody>
</table>

MMP, matrix metalloproteinase; VCAM-1, vascular cell adhesion molecule-1.

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**Figure 1.** Pathological background of the features of vulnerable atherosclerotic lesions used for invasive plaque imaging.
cells covering atherosclerotic plaques. As yet there have been very few clinical studies targeting the role of plaque erosion in the development of ACS, except for a few case reports using optical coherence tomography (OCT). Further research in both basic and clinical fields will be needed to precisely define plaque erosion and to determine its clinical significance.

Calcified Nodules
Calcified nodules are a type of vulnerable plaque that accounts for approximately 2–7% of all coronary events. These nodules are defined pathologically as fibrocalcific plaque with disruption of the luminal surface, little or no underlying necrotic core, and thrombus formation overlying the calcified surface and protruding into the vascular lumen. The underlying plaque is usually characterized by heavy calcification and large plates of calcified matrix with surrounding areas of fibrosis, inflammation, and neovascularization. Interestingly, pathological examination has shown that these lesions are found predominantly in the mid-right coronary artery, where coronary torsion stress is maximal. Intravascular ultrasound (IVUS) and OCT examination are able to diagnose calcified nodules in the coronary arteries. Although the calcified nodule has been categorized as a vulnerable plaque, a recent prospective clinical study using 3-vessel IVUS reported that this nodule type was not a predictor for major adverse events during 3 years of follow-up.

Natural History of Vulnerable Plaque
The abovementioned pathological findings regarding vulnerable plaque have been obtained primarily in the context of autopsy studies. Coronary specimens are retrospectively analyzed after event occurrence, so it is difficult for pathological studies to investigate longitudinal changes in vulnerable plaques, as well as the baseline plaque morphologies, that cause future development of coronary events. Only imaging technologies in clinical practice are able to observe the natural history of coronary plaques with vulnerable characteristics.

A recent clinical study using serial virtual histology IVUS (VH-IVUS) reported that 75% of TCFA healed and 25% of TCFA maintained baseline characteristics during a 12-month follow-up. It is important to note that not all vulnerable plaques progress to rupture, although the mechanism of TCFA healing is not well established.

Motoyama et al performed computed tomography (CT) angiographic examinations in 1,059 patients and prospectively followed them for 27 months for the development of ACS. Coronary lesions were analyzed for the presence of 2 features indicating plaque vulnerability: positive remodeling (lesion diameter at the plaque site ≥10% larger than that of the reference segment) and low-attenuation plaques (non-calcified plaques with a density <30 Hounsfield units). Although these features are not completely consistent with pathological studies, ACS developed in 22% of patients who had plaques with both vulnerability features at baseline, compared with 0.5% of patients who had plaques without these features. None of the patients with normal CT angiography developed ACS. The presence of 1- or 2-feature positive plaques was the only significant independent predictor of ACS.

Invasive Imaging Modalities
Current invasive imaging technologies differ in their ability to image the various morphological features marking coronary plaque vulnerability. Table 2 summarizes these differences.

IVUS
Conventional grayscale IVUS has been used in catheterization laboratories for over 20 years. It is an established modality used not only for guidance during percutaneous coronary intervention (PCI), but also, in the context of clinical studies, for evaluating the tissue characteristics of coronary plaques and assessing plaque progression or regression. Its ability to provide precise qualitative and quantitative measurements of total plaque area and volume (burden), even in cases of positive vascular remodeling, make it invaluable for evaluating the vulnerability of coronary plaques. IVUS has been also used to demonstrate the relationship between cholesterol levels and percent atheroma volume, as well as the role of statin drugs in plaque regression.

However, because conventional IVUS is limited by a relatively low spatial resolution (100–150 μm) and cannot accurately differentiate plaque components, several novel methods such as VH-IVUS have been developed to analyze acoustic signals before demodulation and scan conversion (radiofrequency data).

The use of IVUS to investigate the vulnerability of coronary plaques has been producing increasing amounts of data. In the recent longitudinal, multicenter PROSPECT study, 693 ACS patients were evaluated using 3-vessel grayscale and VH-IVUS, and the relation between baseline IVUS characteristics of culprit and nonculprit plaques and the secondary occurrence of major adverse cardiovascular events (MACE) at 3 years was studied. In this patient population, the MACE rate during the 3 year follow-up was 20.4%, and these events were equally attributable to the progression of nonculprit lesions and to

### Table 2. Comparison of Invasive Imaging Modalities for Vulnerable Plaque Characterization

<table>
<thead>
<tr>
<th>Imaging source</th>
<th>Grayscale IVUS</th>
<th>VH-IVUS</th>
<th>OCT</th>
<th>Angioscopy</th>
<th>NIRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resolution (μm)</td>
<td>150–200</td>
<td>150–200</td>
<td>10–15</td>
<td>50</td>
<td>1,000</td>
</tr>
<tr>
<td>Lipid pool</td>
<td>*</td>
<td>***</td>
<td>***</td>
<td>**</td>
<td>None</td>
</tr>
<tr>
<td>Calcium</td>
<td>***</td>
<td>***</td>
<td>***</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Fibrous cap</td>
<td>*</td>
<td>**</td>
<td>***</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Macrophage</td>
<td>None</td>
<td>None</td>
<td>*</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Microvessel</td>
<td>None</td>
<td>None</td>
<td>**</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Thrombus</td>
<td>*</td>
<td>*</td>
<td>***</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

*Modest; **good; ***excellent.
index culprit lesions treated by PCI. For MACE related to nonculprit lesions, no angiographic variables were associated with subsequent events. By contrast, the following IVUS and VH-IVUS baseline plaque parameters independently predicted the subsequent development of nonculprit lesion-related MACE: large plaque burden (≥70%), higher stenosis rate (minimal luminal area ≤4.0 mm²), or the presence of VH-IVUS-detected TCFA. In addition, no events developed in coronary plaque segments with <40% plaque cross-sectional area. A higher number of positive plaque parameters was accompanied by a higher MACE rate. However, even when all 3 predictive variables were present, the event rate rose to only 18.2%, indicating that although IVUS-derived characteristics suggest the occurrence of a subsequent event, they are not sufficient to predict which atheromas will undergo plaque progression. It is possible that the relatively low spatial resolution of IVUS failed to differentiate fine vulnerable structures in atheromatous nonculprit lesions, and that integration of systemic factors that influence plaque biology is necessary for more precise estimation of future ACS development.

Recently, newer technologies based on novel analysis of raw acoustic signals have been introduced into clinical practice, including virtual histology, integrated backscatter analysis of radiofrequency, strain and elasticity mapping, palpography, and high-definition IVUS that utilizes 60-MHz ultrasound.56–58 The clinical value of these new modalities is yet to be evaluated.

**OCT**

OCT is a relatively new high-resolution intracoronary imaging technology based on near-infrared interferometry. The spatial resolution of OCT, nearly 10 μm on the lateral axis, is almost 10-fold higher than that of conventional IVUS. The higher pull-back speed of frequency domain OCT can prevent heart motion artifacts and thus allow precise assessment of the longitudinal distribution of plaque components. The tissue characterization ability of OCT in coronary atherosclerotic lesions has been well validated in clinicopathological studies.59–61 Because of its excellent spatial resolution, OCT is currently the only imaging technology that can precisely measure the thickness of the fibrous cap and also directly visualize microvessels within coronary atherosclerotic plaques. Furthermore, OCT is able to identify macrophage infiltration in the plaque, an important feature of continuous inflammation in TCFA.62–64 (Figure 2) The other advantage of OCT is its ability to detect intracoronary thrombi that are not usually well visualized by other imaging modalities. OCT not only visualizes thrombi, but can also distinguish between red and platelet-rich white thrombi.63

In patients with CAD, TCFA has been detected by OCT in 72% of cases of ST-elevation MI (STEMI) and 50% of patients with non-STEMI culprit lesions, as compared with 20% of patients with stable angina pectoris lesions; the fibrous cap thicknesses in these 3 groups were reported to be 47, 54, and 103 μm, respectively.60 Furthermore, OCT examination after thrombus aspiration in patients with ACS revealed that 73% of them had plaque rupture, and the mean thickness of the ruptured fibrous cap was 49 μm.64 These OCT observations in patients with ACS correspond well to established pathological findings of vulnerable plaques that resulted in coronary events.

The rate of secondary cardiovascular events is substantially higher in patients with previous ACS than in those with stable angina. OCT examination revealed that compared with nonculprit plaques in non-ACS patients, nonculprit plaques in ACS patients had a wider lipid arc, a longer lipid length, a thinner fibrous cap, and a higher prevalence of neovascularization, suggesting that nonculprit plaques in ACS patients are more vulnerable than in non-ACS CAD patients.65–66

The major drawback of OCT is the relatively shallow penetration of light into the vascular wall, which necessitates the use of other modalities, such as IVUS and coronary CT, to evaluate total plaque volume and vessel remodeling. Although OCT seems to hold promise for evaluating the vulnerability of coronary atherosclerotic lesions, there have not yet been any prospective studies of the role of OCT-derived vulnerable plaques in the occurrence of future ACS. However, in a small group of patients, baseline OCT findings of microchannels

**Figure 2.** Plaque characterization of non-stenotic coronary atherosclerotic lesions with optical coherence tomography. (A) Normal coronary artery, (B) stable fibrous plaque, (C) thick-cap fibroatheroma (arrows indicate thickness of fibrous cap), (D) thin-cap fibroatheroma (arrows indicate thickness of fibrous cap), (E) macrophage infiltration at the surface of plaque (arrow), (F) plaque neovascularization (arrow), (G) calcium deposition (arrows), (H) possible plaque erosion (arrow), (I) ruptured plaque (arrow indicates disrupted fibrous cap, *false lumen), and (J) intraluminal thrombus (*).
and TCFA were reported to be independent predictors for subsequent angiographic progression of non-stenotic coronary plaques. 65

Recent studies have reported the development of neoatherosclerosis (NA)-type changes inside both bare-metal stents and drug-eluting stents several years after implantation. 13, 14 These changes are assumed to play an important role in the development of the late in-stent restenosis and late stent thrombosis that leads to secondary coronary events related to the culprit lesion. Kato et al recently showed that several factors independently predicted NA, including stent age ≥48 months, drug-eluting stents as opposed to bare-metal stents, current smoking, and chronic kidney disease; in contrast, the use of angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists was a protective factor against NA. 68

OCT imaging may have further diagnostic potential in the concomitant use of functionalized magnetofluorescent nanoparticles (NPs) targeting endothelial markers such as vascular adhesion molecule-1. 69 Cathepsin B-activated NPs were also tested with optical imaging methodologies to monitor plaque inflammation in animal in vivo studies. 70

Angioscopy
Intracoronary angiography can directly visualize the morphology of the luminal surface of atherosclerotic plaques, facilitating the evaluation of features such as intimal rupture and thrombus formation. The technique is also able to semiquantitatively measure the intensity of the yellow color plaques, 71–74 which negatively correlates with fibrous cap thickness. White plaques represent fibrous plaques or lipid plaques with a thick fibrous cap. In contrast, yellow plaques are associated with positive remodeling and thrombus formation. 75–78 and angiography has also indicated a significant correlation with the risk of subsequent coronary events. Yellow plaques with fibrous caps <110 μm thick, as measured by OCT, were identified by angioscopy with a sensitivity and specificity of 98% and 96%, respectively. 73 Serial changes in plaque color have been quantified for use in assessing the efficacy of medical treatments such as statins. 75

Developing New Imaging Technology
Near-Infrared Spectroscopy (NIRS)
NIRS imaging is based on the absorbance of light by organic molecules at wavelengths in the near-infrared spectrum (1,000–2,400 nm), and has been used to characterize the chemical composition of biological tissues. Current NIRS systems use algorithms to calculate the probability of high lipid content in atherosclerotic plaques, and display their results in the form of color-coded maps called chemograms. The ability of NIRS to identify lipid-rich atherosclerotic plaques with high sensitivity and specificity in vitro suggests that NIRS might be used to detect lipid-rich vulnerable plaques in the clinical setting. 76–78

The major limitation of NIRS is that it provides only compositional information, and not data regarding the spatial distribution of the components of the target tissue. Accordingly, the combination of NIRS with conventional IVUS or OCT should compensate for the drawbacks of each modality and improve the ability to diagnose vulnerable plaques. Prospective clinical trials are necessary to establish the role of NIRS in daily clinical practice.

Near-Infrared Fluorescence (NIRF)
Fluorescence spectroscopy measures the short-lived fluorescence that is emitted from a molecule after excitation by light. Although still under investigation, intravascular NIRF imaging using agents with emission wavelengths between 650 nm and 1,000 nm has increased the potential for molecular imaging of atherosclerosis. 79 A number of NIRF imaging agents, such as indocyanine green and protease-activatable agents, have recently been tested in vivo. 80 Recent studies using an experimental model have used catheter-based NIRF to successfully visualize atheroma inflammation, calcification, and angiogenesis. In the near future, NIRF will expand our ability to diagnose vulnerable coronary plaques.

Future Perspectives
Over the past 2 decades, several intracoronary invasive imaging modalities have been developed, and their ability to identify vulnerable aspects of coronary atherosclerotic lesions has been evaluated. However, none of these new technologies is perfect in this regard, and the utilization of any single modality cannot reliably identify vulnerable plaques in current clinical practice. For the present, a combination of these technologies, including both invasive and non-invasive imaging, as well as serum biomarkers, should best compensate for the shortcomings of each approach and maximize the possibility of detecting vulnerable plaques.

This review focused on the role of invasive imaging technologies in vulnerable plaque detection. Clearly, the major limitation of invasive modalities is their intrinsic invasiveness and their consequently limited application to large numbers of CAD patients and populations with atherosclerotic risk factors. It will be important to identify the specific patient population that can benefit most from invasive plaque imaging. In patients with either chronic CAD or ACS who undergo coronary angiography, the use of high-resolution invasive modalities to evaluate the entire coronary tree, including both culprit and nonculprit lesions, will provide important information regarding subsequent strategies for secondary prevention.

In addition to their diagnostic capabilities, intracoronary invasive imaging modalities make it possible to simultaneously treat vulnerable plaques. Preliminary investigations have used a self-expandable device to seal OCT-determined TCFA without causing flow-limiting stenosis. 82 Although long-term results have not been evaluated, local plaque sealing and passivation may stabilize TCFA in high-risk patients with CAD. Furthermore, Waksman et al reported that intracoronary photodynamic therapy with intravenous administration of a macrophage-targeting photosensitizer promoted stabilization of lipid-rich atheromatous plaques in a rabbit model. 83 Combining OCT with the delivery of photosensitizer-activating light holds promise for the simultaneous diagnosis and treatment of macrophage-infiltrating vulnerable plaques.

Conclusions
The focus of this review has been the present and future role of invasive imaging technology in the clinical management of atherosclerotic plaques. Large-scale clinical studies will be needed to show that high-risk plaques identified with these imaging techniques can significantly improve ACS prediction compared with modern clinical practice using conventional biological predictors. In addition, coordinating clinical data obtained by invasive modalities with pathological and clinical laboratory findings will enhance our understanding of CAD and facilitate the future development of entirely new methods of both prevention and treatment. These efforts and further advances in invasive imaging technology will hopefully en-
able us to precisely identify vulnerable plaques and develop more effective treatments for vulnerable patients.

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Disclosures

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