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Multimodality Imaging to Detect Vulnerable Plaque in Coronary Arteries and Its Clinical Application

Pannipa Suwannasom, Yohei Sotomi,
Yosuke Miyazaki, Erhan Tenekecioglu,
Yoshinobu Onuma and Patrick W. Serruys

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Abstract

Postmortem studies have described the association between the thin-cap fibroatheroma (TCFA) and the occurrence of acute coronary syndrome (ACS). Both noninvasive and invasive techniques have been refined and used as a research tool to visualize the plaque at a high risk of disruption. There has been a considerable effort to develop the imaging modalities that offer detailed visualization of coronary pathology and accurately predict the adverse cardiac outcomes. This chapter provides an overview of the current and experimental coronary imaging methods to detect vulnerable plaque and discuss the potential implication of multimodality imaging in clinical practice.

Keywords: vulnerable plaque, imaging, IVUS, OCT, CCTA, CMR

1. Introduction

Cardiovascular diseases are the leading cause of death worldwide. It is predicted that by 2030, the number of deaths from coronary artery disease and stroke will increase from 17.3 million in 2008 to 23.3 million [1]. Current diagnostic strategies emphasize on preventing future coronary events by early identification of the vulnerable patient and modification of the risk by medication. The postmortem data have shown that the coronary events were associated with sudden luminal thrombosis due to plaque rupture. The thin-cap fibroatheroma is the most common constituent of a vulnerable plaque. Consequently, intensive studies in intracoronary imaging have been conducted to demonstrate the relationship between the imaging findings and the cardiovascular events. However, the results from such trials remain

controversial. In this chapter, we summarize the currently available coronary imaging techniques and the ongoing development of imaging technologies that detect vulnerable plaque. The clinical application of multimodalities imaging in detecting vulnerable plaque in clinic also discussed.

2. Definition and terminology of vulnerable plaque

The term “vulnerable plaque” has been established as a nomenclature to describe the instability of the plaque at a high risk of disruption, leading to thrombosis and rapid stenosis progression [2–4]. Retrospective autopsy studies reported that the most common histopathological finding associated with plaque rupture was thin-cap fibroatheroma (TCFA), which accounted for 55–60%, in 30–35% plaque erosion and in 2–7% calcified nodule [5]. However, it should be noted that not all TCFA will rupture, nor will all ruptures lead to a cardiac event [3], but disruption and healing is the mechanism of plaque growth [6] and high-grade stenosis [7]. Consequently, the term “vulnerable patient” has been introduced to indicate the patient who has a high likelihood to develop cardiac events. It remains to be investigated whether we should identify and treat these kinds of vulnerable lesions or patients by coronary intervention before inducing clinical events.

3. Current imaging technique

3.1. Noninvasive imaging to detect vulnerable plaque

3.1.1. Coronary computed tomography angiography

Noninvasive imaging techniques could provide the unique opportunities to evaluate the entire coronary arteries and atherosclerotic plaque beyond luminal narrowing in single examination. Coronary computed tomography angiography (CCTA) has been intensively studied to establish its role for detecting vulnerable plaque and prognostic information of recurrent cardiovascular events.

CCTA has shown its capability to characterize plaque composition similar to intravascular ultrasound (IVUS) by the automated software to quantify the plaque. However, the limited spatial and contrast resolutions of CT preclude the detection of some histological features of vulnerable plaques such as fibrous cap thickness or plaque rupture [8]. Nevertheless, some distinct CCTA morphologies associate with high risk of acute cardiovascular events and should be considered as high-risk plaque: [1] large plaque volume; [2] low CT attenuation plaque (LAP); [3] napkin-ring sign (NRS); [4] positive remodeling (PR) and [5] spotty calcification. The total plaque volume measured by CCTA was independently associated with the coronary events [9, 10]. The patients who develop acute coronary syndrome (ACS) had total plaque volume and total noncalcified plaque volume at baseline higher than those who did not develop ACS (median 94 vs. 29 mm³; $P < 0.001$ and 28 vs. 4 mm³; $P < 0.001$, respectively)

[9]. Low CT attenuation plaques, defined by <30 HU, were frequently observed in patients with ACS [11] and ruptured fibrous cap [12]. Napkin-ring sign is defined as central low-attenuation plaque with a peripheral rim of higher CT attenuation. It has been suggested that napkin-ring sign is the result of differences in CT attenuation between the large necrotic core (a central low CT attenuation) and fibrous plaque tissue (ring-like higher attenuation) [13]. Presence of NRS is strongly associated with future ACS events, independent of other high-risk coronary CTA features (presence of obstructive plaque, positive remodeling, low-attenuation plaque) [14], and also associated with the presence of TCFA defined by optical coherence tomography (OCT) [15]. Postmortem data reported that positive remodeling is associated with a high macrophage count and large lipid core [16]. CCTA-derived remodeling index has a consistent with histopathological data, lesion with positive remodeling (remodeling index ≥ 1.1) on CCTA, are associated with a higher percent of the necrotic core and a higher prevalence of the TCFA assessed by virtual histology intravascular ultrasound (VH-IVUS) than those lesions without positive remodeling [17]. In a retrospective study of 1059 patients who underwent CCTA, patients with positive remodeling with low-attenuation plaques were associated with high risk of subsequent ACS as compared to those without such features. (HR: 22.8, 95% CI: 6.9 to 75.2, $p < 0.001$) [9]. Spotty calcification on CCTA is defined as a small, dense (>130 HU) plaque component surrounded by noncalcified plaque tissue and size <3 mm. Small spotty calcification (<1 mm) was related to vulnerable plaque features defined by VH-IVUS [18]. From all of the above features, CCTA would be considered as a tool to detect vulnerable plaque in the future.

3.1.2. Cardiac magnetic resonance (CMR) imaging

Compared with CCTA, cardiac magnetic resonance (CMR) identifies coronary stenosis $>50\%$ comparable to CCTA [19] where it could provide a superior in defining soft tissue such as positive remodeling and increased coronary wall thickness [20]. High-intensity coronary signal on T1-weighted MRI is associated with vulnerable morphology [21, 22] and future cardiac events. It has been demonstrated that high-intensity signal is related to the formation of methemoglobin during subclinical plaque rupture or hemorrhage [23]. T2-weighted short inversion recovery sequences have shown their ability to detect coronary wall edema relating to culprit ACS lesions [24]. However, coronary assessment by CMR is hampered by an inherent susceptibility to motion artifact from prolonged acquisition time [25] that limits its application in clinical practice.

3.1.3. Combined positron emission tomography (PET)-CCTA

Despite the fact that CCTA and MRI demonstrate morphological characterization of plaque, they could not quantify the degree of plaque inflammation. The positron emission tomography (PET) has been combined with computed tomography to identify the anatomical and degree of inflammation. Although ^{18}F -fluorodeoxyglucose (FDG) is acknowledged as conventional tracer in this field, it is hampered by significant myocardium uptake [26] and arterial wall with inflammation. To avoid the myocardial metabolism artifact, ^{18}F -sodium fluoride (NaF) has been introduced to circumvent the myocardial uptake issue. ^{18}F -NaF could localize individual

coronary plaque with minimal background uptake. ^{18}F -NaF is a useful tool to detect molecular calcification which closely linked to plaque rupture. It also provides reliable identification and localization ruptured and high-risk coronary plaque in post-MI setting [27]. The ongoing trials (PREFFIR, NCT02278211 and NCT02110303) aim to investigate the prognostic value of ^{18}F -NaF coronary microcalcification to predict the progression and recurrent of events.

3.2. Invasive imaging to detect vulnerable plaque

3.2.1. IVUS and its derivatives

3.2.1.1. Grayscale IVUS

Grayscale IVUS (GS-IVUS) provides robust information of vessel dimension, lumen dimension, phenotype and distribution of the plaque. GS-IVUS has been incorporated in the guideline as a supporting tool to guide percutaneous coronary intervention in selected lesions [28]. It has been reported that increase plaque burden is associated with adverse cardiovascular outcomes [29]. The major drawback of GS-IVUS is the imprecision to detect lipid-rich plaque which is a marker of the plaque vulnerability [30]. Several GS-IVUS features have been reported that they linked to high risk for cardiovascular events: *Echo-attenuated* plaque was identified by the absence of the ultrasound signal behind plaque that was either hypoechoic or isoechoic to the reference adventitia without calcification [31]. This feature indicated the presence of a large NC or lipid pool, and the closer the attenuation was to the lumen, the more advanced of NC [32]. *Echolucent plaque* contained an intraplaque zone of absent or low echogenicity surrounded by tissue of greater echodensity. Echolucent zone indicated the presence of a relatively smaller NC or lipid pool compared with echo-attenuated plaque [32]. *Spotty calcification* contained small calcium deposits within arcs of $<90^\circ$. IVUS spotty calcification is closely related to the presence of an NC, also indicating plaque instability [32].

Besides the ability to demonstrate plaque morphology, IVUS was fused with the coronary angiography to reconstruct the blood flow simulation model to examine the local hemodynamic forced on coronary plaque progression. The PREDICTION (Prediction of Progression of Coronary Artery Disease and Clinical Outcome Using Vascular Profiling of Shear Stress and Wall Morphology) Study, which is done in 374 patients with ACS, showed that the large plaque burden and low local endothelial shear stress (ESS) are independent predictor of plaque progression and lumen narrowing with positive predictive value of 41% [33].

3.2.1.2. Virtual histology intravascular ultrasound

Due to the limited ability of IVUS to determine the composition of plaque, the IVUS radiofrequency analysis (virtual histology, VH) has been introduced to characterize the plaque components. The main difference between GS-IVUS and VH-IVUS is that the GS-IVUS imaging is formed by the envelope (amplitude) of the radiofrequency signal, whereas VH-IVUS analysis uses several additional spectral parameters to identify four tissue types [34, 35]: fibrous (dark green), fibrofatty (yellow-green), necrotic core (red) and dense calcium (white). VH-IVUS-derived TCFA is defined by necrotic core-rich ($>10\%$ of the cross-sectional area) plaque being

in contact with the lumen and with a percent plaque volume of 40% seen on at least three consecutive images [36]. The Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) trial [37] reported the efficacy of VH-IVUS in predicting lesions that will progress and cause cardiovascular events in 697 patients with ACS. The investigators reported that plaque burden of 70% or greater, minimal lumen area of 4.0 mm² or less, and TCFA phenotype were associated with recurrent events after a median of 3.4 years of follow-up with a positive predictive value of 18.2%. The similar trend was reported in VIVA (VH-IVUS in Vulnerable Atherosclerosis) trial, and nonculprit TCFA phenotype was associated with nonrestenotic MACE, on both individual plaque and whole-patient analysis [38].

3.2.1.3. Intravascular ultrasound near-infrared spectroscopy

Near-infrared spectroscopy is an analytical technique that is used in science and industry to determine the chemical composition of substances [39]. A sample of interest is illuminated with near-infrared (NIR) light (800–2500 nm in wavelength) which is absorbed by C–H, O–H and N–H bonds. Each given molecule has a unique pattern of absorption known as its spectroscopic fingerprint. Therefore, NIRS could provide sample recognition and tissue classification [40]. NIRS has been applied to the catheter-based device to identify and quantify lipid cores which is the major composition of the TCFA, the most common type of vulnerable plaque [5]. In addition, NIRS can image through calcium, whereas conventional IVUS, VH-IVUS and OCT are not capable. The current intravascular ultrasound near-infrared spectroscopy (IVUS-NIRS) catheter, TVC Imaging System™ (InfraRedx Inc. Burlington, MA, USA), is CE (Conformité Européenne) marked and has an FDA clearance for lipid core-containing coronary plaques (LCP) detection. The information from the catheter will be processed via mathematical algorithm that predicts the probability of vulnerable plaque and are displayed on a chemogram, with lipid pools colored yellow in a background of red [39]. The “block chemogram” provides visual interpretation of the algorithm probability from zero to one for likelihood of LCP in the corresponding 2-mm chemogram segment (yellow $P > 0.98$, tan $0.84 \leq P \leq 0.98$, orange $0.57 \leq P < 0.84$ and red $P < 0.57$) [3]. The lipid core burden index (LCBI) represents the lipid burden in a vessel segment. LCBI is the fraction of valid pixels within the scanned region that exceed an LCP probability of 0.6 per million (% multiplied by 1000) [40]. The maxLCBI_{4 mm} indicates sites of high lipid accumulation and is defined as the LCBI of the most lipid-rich 4-mm area within the segment of interest [39]. It should be noted that NIRS could provide only information about lipid core plaque, but it is not able to evaluate the depth and the volume of lipid core.

The autopsy-based study has shown that catheter-based NIRS system accurately identified LCP and IVUS-NIRS system significantly improved the sensitivity for detecting a histological fibroatheroma, especially in calcified lesions and lesions with a smaller plaque burden [41]. The data from diabetic/hypercholesterolemic animal model showed that IVUS-NIRS imaging detected and predicted future development of high-risk coronary lesions such as increased plaque and necrotic core areas, thinned fibrous cap, increased concentration of activated inflammatory cells and apoptotic cells within the fibrous cap [42, 43]. Recently, Oemrawsingh et al. has reported that coronary LCBI in patients with stable angina pectoris (SAP) or acute

coronary syndrome (ACS) is associated with 1-year adverse cardiovascular events throughout the entire coronary tree and not necessarily at the imaged segment or a lesion-specific risk [44]. Madder et al. reported that detection of LRP at nonstented sites was also associated with an increased risk of future major adverse cardiovascular events [45]. The ongoing PROSPECT II (NCT02171065), the Lipid-Rich Plaque (NCT02033694) [46] and ORACLE-NIRS (NCT02265146) will support the concept of vulnerable patient identification and may improve a better care in such patients.

3.2.1.4. *Intravascular photoacoustic imaging*

Intravascular photoacoustic imaging (IVPA) is an analytic technique, which is highly specific for lipid type. The principle of photoacoustics is based on the optical contrast which is provided by the differences in the absorption spectra of plaque components to image plaque composition [47], like NIRS. However, it has depth resolution, which makes IVPA possible to know the exact spatial location of the lipids within the plaque relative to the lumen border [47]. Lipid in the plaque mainly consists of cholesterol and cholesterol esters, whereas pericardial fat is stored as mixture of fatty lipid. IVPA could differentiate between lipid in the plaques and periadventitial fat. It is postulated that this modality would offer detailed assessment of plaque vulnerability and evaluation of the pharmacologic plaque modulation in future clinical studies. However, the hurdle of IVPA is that the image quality drastically deteriorates in the presence of the luminal blood that may require blood clearance during image acquisition [47]. The clinical application of IVPA remains to be demonstrated in clinical studies.

3.2.2. *Optical coherence tomography and its derivatives*

3.2.2.1. *Optical coherence tomography*

OCT uses low-coherence, near-infrared light (1.3 μm wavelength) emitted through a fiber optic wire with rotating lens [48]. The image is created based on reflection time and the intensity of the backscattered light [49]. The resolution of OCT image (10–20 μm axial and 20–40 μm lateral) allows precise visualization of the plaque morphology [48, 50]. It also enables the measurement of fibrous cap thickness [51, 52]. Another unique ability of OCT is identification of macrophages, which are relatively large (20–50 μm) [53], neovascularization [54–56] and microcalcifications [48].

Due to its limited tissue penetration (1–3 mm), it remains impossible to precisely assess the deeper layers behind light-attenuating plaques and thus accurate plaque volume. The imaging artifacts also lead to the misclassification of the stable plaque type to high-risk plaque type. For instance, tangential artifact can mimic superficial accumulation of macrophages or necrotic core [48, 57]. It has been demonstrated that not all bright spots are caused by macrophages and only 23% of bright spots represent macrophages. Other sources of bright spots can be generated by a combination of plaque components that create sharp changes in the index of refraction [58].

Besides the direct assessment of the plaque morphology, OCT also allows vascular profiling of coronary arteries that enables microenvironment study within the coronary arteries [59]. The advancement of computed fluid dynamic (CFD) in combination with precise OCT images

extends our current understanding of endothelial shear stress (ESS). OCT-based assessment of local ESS in nonculprit arterial regions of 21 patients presenting with acute coronary syndrome has shown that segments with low ESS (< 1 Pa) had higher prevalence of lipid-rich plaques (37.5 vs. 20.0%; $P = 0.019$) and thin-cap fibroatheroma (12.5 vs. 2.0%; $P = 0.037$) compared with segments with higher ESS (≥ 1 Pa) [60]. Additionally, areas with low ESS as compared to those with high ESS showed larger lipid accumulation, thinner fibrous cap, and greater macrophage density, which would contribute to plaque vulnerability [60].

3.2.2.2. Optical coherence tomography and near-infrared spectroscopy

Although OCT could provide excellent image resolution, its limitation is the light penetration depth and the capability to detect the plaque composition. The optical coherence tomography and near-infrared spectroscopy (OCT-NIRS) system utilizes a wavelength-swept light source for both OCT and NIRS. The catheter collects the backscattered OCT light together with the chemical substances from the plaque residing within the arterial wall [61]. Therefore, it will eliminate the uncertainty of plaque-type interpretation and will facilitate identification of the high-risk plaque location.

3.2.2.3. Optical coherence tomography and near-infrared autofluorescence (OCT-NIRAF)

Several intracoronary imaging methods have been developed to visualize plaque. However, those techniques could not provide the status of inflammation. Therefore, the molecular imaging of atherosclerosis has been studied to address the inflammatory activity, macrophage composition, presence of fibrin, cellular apoptosis and neoangiogenesis [62]. One of the molecular imaging-based approaches is near-infrared fluorescence (NIRF) [63]. The NIRF can detect the deposition of the indocyanine green (an FDA-approved NIRF-emitting compound) in lipid-rich and atherosclerotic plaques [64].

Due to the requirement of exogenous agent in NIRF technique, the “near-infrared autofluorescence (NIRAF)” has been developed to detect fluorescence from naturally occurring molecules. It has been reported that the combination of OCT and red-excited NIRAF (633 nm) with emission detected between 700 and 900 nm can be used to detect necrotic core and TCFA in cadaver coronary arteries [65]. Recently, Ughi et al. report the first-in-man study of optical coherence tomography and near-infrared autofluorescence (OCT-NIRAF) in 12 patients undergoing percutaneous coronary intervention. They showed that OCT-NIRAF was as safe as conventional OCT in terms of the capability to provide automatic and facilitated image interpretation [66].

3.2.2.4. OCT light property analysis

Despite the excellent resolution of OCT, the image interpretation of plaque morphology based on qualitative criteria can be ambiguous and time-consuming. To overcome those limitations, the automatic classification of atherosclerotic plaque and quantitative assessment of tissue characteristics with OCT light property analysis are investigated. Light property has three components: light intensity, light attenuation and backscatter. The light intensity indicates the amount of light signal detected at a certain location in the vessel wall based on reflection and

backscatter. The light attenuation, estimated as the depth-resolved attenuation coefficient, indicates how fast the light signal decays. It is the rate of exponential decreasing intensity related to the light propagation depth. The backscatter, estimated as the depth-resolved backscattering coefficient, is related to the efficiency of light scattering in the tissue [67].

In ex vivo validation experiments, highly attenuating regions (attenuation coefficient $\mu_t \geq 8 \text{ mm}^{-1}$) have been associated with necrotic core or macrophages. Conversely, low attenuating regions $\mu_t < 6 \text{ mm}^{-1}$ were associated with healthy vessel, intimal thickening or calcified plaque [68, 69]. Thus, by using light attenuation analysis, it could detect the lipid-rich plaque component.

Liu and colleagues extended the light property analysis with light intensity and backscatter in addition to the light attenuation analysis [67]. They evaluated the light property values in each tissue type (fibrous, lipid, calcium, calcium with lipid, macrophages and necrotic core) in histology-matched OCT images and found that all tissue types have their own spectrum of light property, suggesting the possibility of automatic tissue characterization with OCT light property analysis in the near future.

4. Clinical application of multimodality imaging in detecting vulnerable plaque

4.1. Assessment of the effect of pharmacotherapy on plaque modulation

OCT has been used to evaluate the plaque stability by statin therapy, and an increase in fibrous cap thickness in coronary plaques was observed after the treatment [70, 71]. Recently, IVUS has been used to evaluate the effect of proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors on the progression of coronary atherosclerosis in statin-treated patients. PCSK9 inhibition with evolocumab was associated with a reduction in percent atheroma volume for evolocumab (−0.95%) but not placebo (+0.05%) and a greater percentage of patients demonstrating plaque regression (64.3 vs. 47.3%) [72].

4.2. Assessment of the effect of local therapy on vulnerable plaque

Previously, bioresorbable scaffold (BRS) has been investigated for the capability of sealing superficial plaque [73–75]. The neointima on top of the BRS struts altered the plaque phenotype by covering the calcific spots and TCFA, thus transforming the TCFA to thick-cap fibroatheromas that associate with the plaque stability without compromising the luminal dimensions [73]. It has been speculated that BRS may prevent the cardiac adverse event by invasive sealing of the high risk to rupture plaques. The ongoing PROSPECT ABSORB (NCT02171065) trial will examine the treatment of vulnerable plaques with the ABSORB bioresorbable vascular scaffold (BVS) plus guideline-directed medical therapy (GDMT) in comparison with GDMT alone [76]. All randomized patients will undergo 2-year follow-up angiography with three-vessel repeat NIRS-IVUS imaging, thus enabling evaluation of plaque regression/progression in intervening vessels and nonintervening vessels [77]. The

SECRITT-II study will investigate the ability of BVS to expedite the process of de novo fibrous cap formation in comparison with high-dose statin therapy [77].

5. Future perspective

Aside from the technical issues and validity of each imaging modality in detecting vulnerable plaque, and predicting the future events, a real question is whether identification of vulnerable plaque would have any impact on our practice [78–80]. Although it has been demonstrated that VH-IVUS TCFA is able to predict recurrence of events, the positive predictive value was 18% [37] with the risk of catheter-related complication of 0.6–1.6% [33, 37]. Thus, the improvement of imaging technologies is required to provide complete and detailed evaluation of plaque morphology, physiology, and biology to predict the future events [81]. New hybrid catheters have shown their capabilities in demonstrating the plaque vulnerability; however, the clinical benefit needs confirmation by larger studies. Noninvasive technique, especially CCTA combined with PET, may support the detection of vulnerable plaque and tailoring the treatment of those patients.

6. Conclusion

Either noninvasive or invasive imaging techniques have their unique properties in detecting the vulnerable plaque; however, none of the individual imaging techniques is able to provide complete plaque assessment. There has been a considerable effort to develop the imaging modalities that offer detailed visualization of coronary pathology and accurately predict the adverse cardiac outcomes. Combination of imaging techniques in single examination would provide mechanistic insight into the development and pathophysiology of the vulnerability of the plaque. To translate imaging information into clinical application, it requires randomized trials investigating whether interventions according to the imaging findings can improve clinical outcomes, along with an intensifying improvement of imaging technologies.

List of abbreviations

CCTA	Coronary Computed Tomography Angiography.
CE	Conformité Européenne.
CI	Confident Interval
CMR	Cardiac Magnetic Resonance Imaging.

FDA	Food and Drug Administration (US).
HR	Hazard Ratio.
MACE	Major Adverse Cardiac Events.
MI	Myocardial Infarction.
NC	Necrotic Core.
LCB	Lipid Core Burden Index.
LCP	Lipid Core-containing coronary Plaques.
LRP	Lipid-Rich Plaques.
SECRITT	vShield Evaluated at Cardiac Hospital in Rotterdam for Investigation and Treatment of TCFA.

Author details

Pannipa Suwannasom¹, Yohei Sotomi^{2,3}, Yosuke Miyazaki⁴, Erhan Tenekecioglu⁴, Yoshinobu Onuma^{4,5} and Patrick W. Serruys^{6*}

*Address all correspondence to: patrick.w.j.c.serruys@pwserruys.com

1 Northern Region Heart Center, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand

2 Academic Medical Center, Amsterdam, The Netherlands

3 Department of Cardiology, Osaka Police Hospital, Japan

4 Erasmus Medical Center, Rotterdam, The Netherlands

5 Cardialysis, Rotterdam, The Netherlands

6 Imperial College London, London, United Kingdom

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