

Update on Clinical Imaging of Coronary Plaque in Acute Coronary Syndrome

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Abstract

Current evidence suggests that understanding coronary artery disease extends beyond identifying and treating traditional risk factors. Progression of coronary plaque contributes to the development of acute coronary syndrome (ACS). In this article, we reviewed current literature for modalities to image coronary plaque as well as discussed the role of emerging techniques that can improve our understanding of the pathophysiology of ACS.

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Introduction

Acute coronary syndrome (ACS) encompasses the clinical spectrum of unstable angina (UA) and acute myocardial infarction (AMI). Most ACS are precipitated by luminal thrombi within coronary arteries, which may arise from 3 different atherosclerotic plaque morphologies: plaque rupture, plaque erosion or calcified nodules.¹ Plaque rupture is the underlying cause in 60% to 75% of cases and is hypothesised to involve disruption of a vulnerable plaque that consists of a thin fibrous cap heavily infiltrated by macrophages and T lymphocytes, hence exposing the underlying necrotic core. An obstructive luminal thrombus develops when the thrombogenic material released from the necrotic core comes into contact with circulating platelets.²

Vulnerable Plaque and Pathophysiology

The term “vulnerable plaque” is used to define thrombosis-prone plaques and plaques with a high probability of undergoing rapid progression.³ The “vulnerable patient”, on the other hand, is used to define patients who are susceptible to an ACS or sudden cardiac death based on plaque characteristics, blood or myocardial vulnerability.³

While advances in medical therapy and novel interventional cardiology techniques have significantly decreased the morbidity and mortality caused by coronary atherosclerosis, identification and treatment of vulnerable plaques and vulnerable patients can potentially improve our management of coronary artery disease. Efforts are

needed to carefully quantify an individual’s risk of an event depending on their overall vulnerability.

Several criteria have been proposed for defining the vulnerable plaque. Major criteria for vulnerability include plaques that are undergoing active inflammation with high macrophage content, thin-cap plaques with large lipid core, fissured plaques or presence of endothelial denudation with superficial platelet aggregation. Superficial calcified nodules, yellow plaque or the presence of intraplaque haemorrhage or outward remodelling form minor criteria for vulnerability.³

Although coronary angiography illustrates luminal narrowing, it does not provide direct information on the changes within the vessel wall or plaque characteristics. Hence, there is widespread interest in alternative modalities, either invasive or non-invasive, to directly visualise arterial wall and characterise plaque composition.

Recent advances in imaging techniques have allowed us to explore and understand the pathophysiology of plaque vulnerability that may lead to the development of novel therapies.

Non-invasive Modalities

Computed Tomography Coronary Angiography

Multi-detector row computed tomography angiography (MDCTA) is an imaging modality that provides assessment of vessel anatomy and atherosclerotic plaque composition

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and morphology. Computed tomography angiography is able to define plaque vulnerability by differentiating between calcified and non-calcified plaques⁴ as well as to categorise coronary plaques into lipid-rich, fibrous, or calcified types based on density measurements.⁵ Figure 1 demonstrates images acquired using a 320-slice MDCTA.

Several limitations exist in the routine use of MDCTA to detect plaque morphology. Use of iodinated contrast to image the coronary tree may increase the procedural risk in patients with impaired renal function or severe heart failure. Current MDCTA protocols are also limited by motion-related image artefacts and inadequate resolution to visualise plaque components. Modifications to MDCTA technique such as increasing number of detector rows, faster rotation gantries, more sophisticated image reconstruction algorithms and the ability to acquire even thinner slices will be required to overcome limitations in precisely determining plaque area, volume and remodelling.⁶

Positron Emission Tomography (PET)

Development in PET technology and instrumentation has occurred rapidly during the last 20 years, driven by the requirement for improved resolution and image quality necessary for clinical and research applications.⁷ The current role of PET in cardiovascular imaging is predominantly targeted at assessment of myocardial ischaemia and viability.⁸

Recent studies have investigated the use of fluoro-deoxyglucose (FDG)-PET to image atherosclerotic plaque inflammation in animal and human models.⁹ FDG signals originate from activated macrophages within the lipid core and fibrous cap of the plaque. It has been shown that there is correlation between FDG uptake and plaque macrophage content.^{9,10} Therefore, FDG-PET may have a role in identifying “high-risk” plaque with high macrophage content and signs of active inflammation.¹¹

Despite the success of cardiac PET in research settings, widespread clinical utility of this modality is hampered by availability of this technology and PET radiopharmaceuticals, its relative high cost as well as limited clinical data to support its routine use.¹²

Magnetic Resonance Imaging (MRI)

MRI uses magnetic field and radiofrequency pulses to obtain high quality images with excellent reproducibility, field of view and speed.¹³ Cardiovascular MRI has grown considerably in recent years in both clinical and research cardiology. However, the use of MRI to identify lipid in coronary plaques is limited by the small size of the target, cardiac motion artefact and lower spatial resolution that makes optimal characterisation of coronary plaques elusive.¹⁴ Furthermore, considerable length of time required

for each study renders routine screening impractical.

Ongoing research exploring the use of alternative contrast agents could further improve the detection of vulnerable plaque and allow us to monitor the efficacy of anti-atherosclerotic therapies.¹⁵ Contrast agents such as gadopentetic acid (Gd-DTPA) may be useful for plaque characterisation while other specific imaging probes targeted to biochemical and cellular markers of atherosclerotic plaque vulnerability¹⁶ may allow for evaluation of plaque composition at a cellular and molecular level.

Invasive Modalities

Intravascular Ultrasound (IVUS) and IVUS with Virtual Histology

Coronary IVUS was made possible by the miniaturisation of ultrasound transducers sited at the tip of very small diameter catheters that could be placed into coronary arteries during percutaneous coronary intervention to quantify the degree of coronary stenosis, localise and determine plaque burden.¹⁷ Visual interpretation of echogenicity on conventional IVUS gray-scale images has been used to provide information on plaque characteristics¹⁸ (Fig. 2). Studies in autopsy specimens have shown that hypoechoic areas represent plaques with increased lipid content, low-intensity or “soft” echoes represent fibromuscular lesions, and moderately hyperechoic areas are associated with fibrous plaques.¹⁹ Calcified plaques will produce a bright ultrasonic reflection on IVUS. However, the association of calcification with plaque vulnerability is complex. Although calcification is associated with atherosclerosis, the plaques causing ACSs have less calcium than those causing stable angina.²⁰ In contrast, a spotty calcium pattern of calcification that has been found more often in culprit lesions of patients with myocardial infarction than in those with stable angina, may be an indicator of vulnerability.²¹

To overcome the challenges of conventional gray-scale IVUS, spectral analysis of radiofrequency ultrasound backscatter signals was developed to assess plaque composition in detail.²² Various real-time determinations of plaque components using IVUS signals with matched histology results have shown that spectral analysis has between 80% to 92% in vitro and 87% to 97% in vivo accuracy when used to identify the 4 different types of atherosclerotic tissue: fibrous, fibrofatty, dense calcium, and necrotic core.^{23,24} While IVUS has been shown to achieve high predictive accuracy in differentiating components of atherosclerotic tissue without thrombus, there are limited studies on its role in assessment of intramural thrombus due to difficulties in differentiating the borderline between intramural thrombus and fibrous plaque.²⁵

The recent PROSPECT (Providing Regional Observations

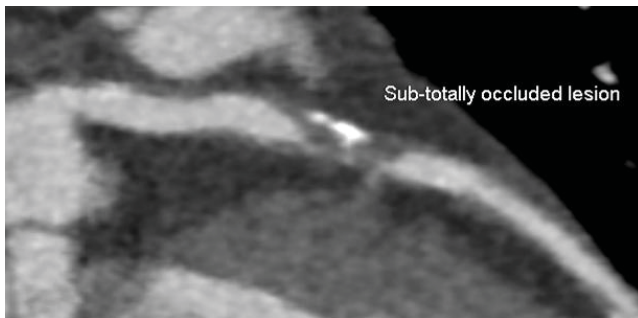


Fig. 1a.

Fig. 1. Coronary artery plaques as shown on multi-detector computed tomography angiogram. (a) A subtotally occlusive plaque with intra-plaque calcification is seen within this left anterior descending artery. (b) Soft eccentric plaque causing mild luminal stenosis is observed in this right coronary artery.

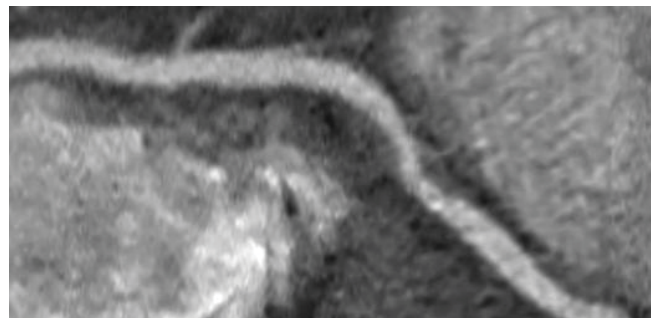


Fig. 1b.

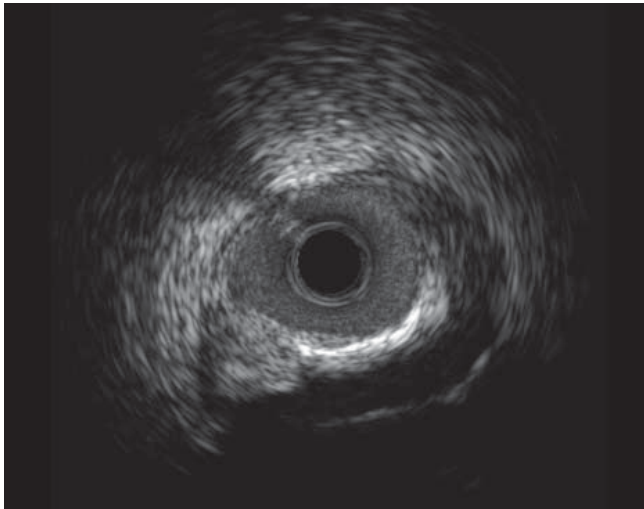


Fig. 2. Eccentric calcified plaque assessed by intravascular ultrasound is seen from 3 to 9 o'clock position in the left main artery.

Table 1. Characteristics of Coronary Microstructures on Optical Coherence Tomography

Histology	Appearance on optical coherence tomography
Intima	Signal-rich layer near lumen
Media	Signal-poor layer in middle of artery wall
Adventitia	Signal-rich outer layer of artery wall
Plaque	Loss of normal wall architecture, narrowed lumen
Fibrous	Signal-rich, homogenous area
Calcified	Well-demarcated, heterogeneous area
Lipid	Signal-poor, poorly-demarcated, homogenous area
Cap	Signal-rich layer overlying signal-poor area

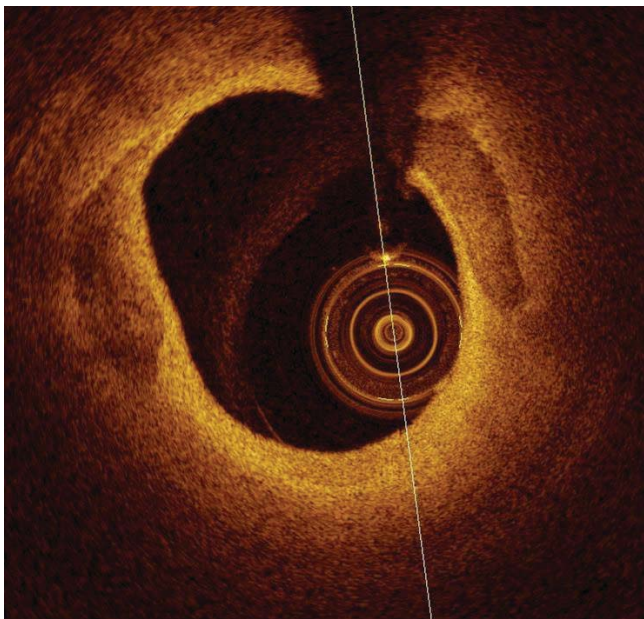


Fig. 3a.

Fig. 3. Images of a left anterior descending coronary artery acquired using optical coherence tomography with Lightlab CX7R OCT system. (a) Image of a coronary vessel with calcified plaque at the 2 o'clock position and a fibrolipid plaque at the 9 o'clock position. (b) Same coronary vessel with coronary stent implanted in a segment with prior in-stent restenosis.

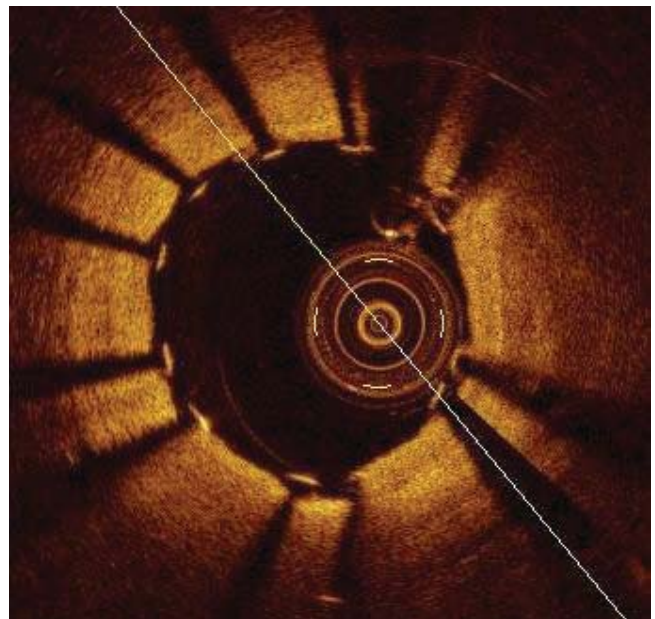


Fig. 3b.

to Study Predictors of Events in the Coronary Tree) trial found that after an ACS, subsequent major adverse cardiac events in a proportion of patients arose from non-culprit lesions with high plaque burden and thin-cap fibroatheromas. This suggests that a combination of IVUS with virtual histology may help identify vulnerable plaques that are associated with adverse clinical outcome (unpublished data – Transcatheter Therapeutics Conference 2009).

Intravascular ultrasound is also valuable for assessing changes in plaque volume in response to anti-atherosclerotic treatments. In a group of patients with stable angina, Kawasaki et al²⁶ reported changes in the radiofrequency IVUS signal consistent with a reduced lipid component indicating plaque stabilisation after 6 months of statin therapy. Studies performed in patients following AMI at baseline and after 6 months showed a decrease in the deformability of plaques, presumably resulting from institution of lipid-lowering therapy.²⁶

Recently, IVUS has been used to study endothelial shear stress produced by coronary artery blood flow.²⁷ The locations of stress have been reported to correlate with the localisation of early plaque, thin cap fibroatheroma and culprit lesions. This technique involves the use of three-dimensional images of the vessel and computational fluid dynamics to calculate the force directed along the endothelial surface of the vessel wall resulting from the friction associated with blood flow.²⁷ Plaque is more likely to originate at sites that have lower shear stress, which predisposes to inflammation and endothelial dysfunction. Hence, detection of this process in the early stages would be of considerable value in predicting the onset of the vulnerable plaque.

Optical Coherence Tomography (OCT)

OCT is a novel high-resolution (4 to 10 microns) in vivo catheter-based intravascular imaging modality capable of identifying coronary plaque characteristics and intra-luminal thrombus.²⁸ An optical analogue of IVUS, OCT measures the intensity of reflected light waves and translates these optical echoes into a high-resolution two-dimensional tomographic image. Figure 3 shows images of a coronary vessel acquired using OCT. Although IVUS is the gold standard for evaluation of coronary plaque, lumen, and vessel dimensions in clinical practice, visual interpretation of conventional gray-scale IVUS cannot reliably differentiate lipid-rich from fibrous plaque nor accurately define intra-luminal thrombus. OCT is currently the only intravascular imaging technique with resolution sufficient to identify thin fibrous cap and lipid rich plaque²⁹ with superior axial resolution when directly compared to IVUS. Its high data acquisition rate allows real-time imaging.³⁰ In histology validation studies, coronary plaque images acquired by OCT

has been correlated with coronary plaque microstructures (Table 1).³¹ In addition, OCT has also been shown to identify intracoronary thrombus as well as distinguish red and white thrombi that corresponds to post-mortem histological examinations.³² The presence of white thrombus has been more frequently associated with UA whereas red thrombus has been implicated in myocardial infarction.³¹ Red thrombi can be identified as high-backscattering protrusions inside the lumen of the artery, with signal-free shadowing in the OCT image; while white thrombi are identified as low-backscattering projections in the OCT image.³¹

It has been recently shown that OCT reflects the macrophage content of the fibrous cap with a high degree of positive correlation between OCT and histological measurements of fibrous cap macrophage density. This potential for fibrous cap characterisation suggests that this technology may be well suited for identifying vulnerable plaques in patients.³³

OCT imaging has been demonstrated to be safe and feasible in patient studies and may potentially be used to optimise percutaneous coronary intervention (PCI) procedures in routine clinical practice. In addition to characterising coronary plaques and thrombus, OCT can demonstrate plaque disruption including tissue prolapse and protrusion after coronary stenting³⁴ and aid with real-time stent apposition and recoil.

A major limitation of OCT is the requirement of a blood-free imaging field because red blood cells scatter light. Using continuous saline flush administration, scanning in vivo at imaging speed of 1 mm/s with previous generation of OCT consoles have restricted the length of vessel segments that can be studied. The application of balloon occlusion catheters to provide a static saline column may allow for scanning of longer vessel segments, but poor tolerance to prolong transient ischaemia during vessel occlusion posed a significant disadvantage to this technique.²⁹ A new generation of OCT console that uses frequency-domain-OCT technology enables images to be acquired at a speed of 15 mm/s³⁵ and permits visualisation of greater vessel length.

An important disadvantage of OCT is poor penetration into non-transparent tissues with visualisation limited to 2 to 3 mm,³⁰ thus allowing evaluation of only superficial structures including coronary plaques with thin-caps. Total lipid pool in deep plaques with large necrotic cores cannot be fully imaged and may require complementary IVUS interrogation.³⁶

Coronary Angioscopy

Coronary angioscopy provides full colour, high-resolution, three-dimensional images and allows direct visualisation of coronary lumen, plaque surface and thrombus. Previous angioscopic studies have shown that disrupted yellow

plaques associated with thrombus formation are frequently identified as culprit lesions in patients with ACS, whereas smooth white plaques without thrombus formation are more frequently found in patients with stable angina or prior myocardial infarction.³² Therefore, the colour and morphology of coronary plaque are proposed to be determinants for plaque stability. In particular, yellow plaques are identified to be more “vulnerable” than white plaque.³⁷

However, significant inter-observer variation exists in interpreting plaque colour, which limits the role of angioscopy compared to other modalities.³⁸ Furthermore, as angioscopy images are restricted to luminal surface, alterations in composition deep within the lesion will not be reflected on the plaque surface, thus reducing the sensitivity of angioscopy in characterising plaque vulnerability.³⁶

Invasive MRI

Invasive MRI techniques have been developed to attempt to quantify components of atherosclerosis in humans.

These novel methods involve insertion of intravascular radiofrequency coils or detectors into coronary catheters and have shown promising results in preliminary work using ex vivo aortic and coronary tissue.³⁹ Although this approach has immense potential in providing excellent data on coronary plaque and thrombus characteristics, its main disadvantage in clinical application is the requirement for patients to be studied in a suite containing an MRI magnet. Further validation on human coronaries is required to establish the role of invasive MRI techniques on coronary plaque analysis.³⁹

Clinical Utility of Plaque Imaging

Table 2 shows an overview of the imaging modalities for plaque characterisation.

As each individual imaging modality is suited to identify different characteristics of plaque, a combination of techniques may be necessary for comprehensive evaluation of the coronary vessel.

For patients with ACS where a more conservative

Table 2. Overview of Imaging Modalities for Plaque Characterisation

Imaging modality	Plaque characteristics detected	Advantages	Disadvantages
Computed tomography	Quantification of calcium burden Lipid component Fibrous components	Non-invasive identification of vulnerable plaques	Contraindicated in renal failure Limited by motion artefacts Inadequate resolution to visualise plaque components Limited by heart rate
Magnetic resonance imaging	Lipid composition of plaque		Cardiac motion artefact Lower spatial resolution Longer length of study time Electromagnetic interference
Positron emission tomography	Plaque macrophage content		Not established for widespread clinical use
Intravascular ultrasound-based methods	Plaque volume Luminal and vessel dimensions Plaque echogenicity Calcification	Good depth of penetration Complements coronary angiography	Lower spatial resolution Difficulty in differentiating the borderline between intramural thrombus and fibrous plaque Invasive
Optical computed tomography	Plaque micro-architecture Accurate measure of cap thickness Plaque disruption and thrombus	High spatial resolution High data acquisition rate	Requires displacement of blood for adequate visualisation Invasive Limited depth of penetration
Coronary angioscopy	Plaque surface visualisation	Three-dimensional Direct visualisation of coronary lumen	Superficial assessment of plaque Yellow colour requires objective determination Requires displacement of blood and causes coronary occlusion
Invasive magnetic resonance imaging	Plaque morphology and structure		Experimental stages Requires apposition of detector to wall and cannot scan the artery

approach is initially adopted by the treating physician, computed tomography of the coronary arteries can provide excellent vessel visualisation and information on vessel characteristics by differentiating between calcified and non-calcified plaques. This can potentially be used to select patients who may benefit from a more invasive treatment approach.

For high-risk ACS patients undergoing invasive treatment, IVUS is a useful tool to assist in PCI as well as identify coronary plaques. When combined with spectral analysis or virtual histology, IVUS has the ability to determine less stable plaque components with high in vivo accuracy. However, as IVUS has inadequate resolution to detect fibrous cap thickness, OCT may be required to definitively detect vulnerable plaque. Therefore, both modalities are complementary and incremental in detecting the “high risk” coronary vessel. Nevertheless, routine application of both modalities during coronary intervention needs to be further evaluated in clinical trials.

In summary, techniques to assess coronary plaque composition and vulnerability are wide-ranging and constantly emerging. Efforts to diagnose and correlate determinants of plaque vulnerability with clinical outcome and cost effectiveness are important to position these imaging modalities as clinical tools in the management of ACS. Future research exploring the predictive value of plaque vulnerability during ACS on future adverse cardiac events will play an important role in identifying high risk patients that require more intensive management.

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