Imaging in Acute Coronary Syndrome

Guest Editors: Alexander Hirsch, Robin Nijveldt, and Igor Klem
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Acute coronary syndrome is a leading cause for hospital admissions both in Europe and the United States resulting in high medical care expenses. During the past 25 years, there have been important advances in the therapeutic options for patients with an acute coronary syndrome with improved medical therapy and the introduction of percutaneous coronary intervention. However, despite the reduction of morbidity and mortality due to various refinements in medical treatment and technology, there are still opportunities to improve outcome in the first months after the event and on the longer run. Accurate recognition of patients that can benefit from additional therapies is, therefore, crucial in the therapeutic management of patients after an acute coronary syndrome.

The standard of care of patients with acute coronary syndrome includes a stepwise approach including different imaging modalities to make a final diagnosis, with rest echocardiography as the most common of the techniques. Recently, new imaging techniques have emerged resulting in a wide array of choices available to cardiologists to improve clinical decision making. These new modalities can be helpful in several aspects including the detection and differential diagnosis of acute coronary syndromes, guiding clinical decision making and improving risk stratification after an event. This is an exciting and a rapidly expanding field of investigation.

In this special issue, several interesting articles in relation to this topic are published for the readership of Cardiology Research and Practice. The first paper is an excellent review by L. Budge and P. Salerno on the role of the cardiovascular magnetic resonance in the evaluation of patients presenting with suspected or confirmed acute coronary syndrome. The authors clearly discuss the role of cardiovascular magnetic resonance in the emergency department for the timely and accurate identification of non-ST-elevation acute coronary syndrome patients. They also highlight the application of cardiovascular magnetic resonance in patients after ST-segment-elevation myocardial infarction because of the identification of complications postmyocardial infarction and the important prognostic information this imaging technique can provide. The second paper is a review by T. Kubo et al. that concerns the current status of optical coherence tomography, a more recently developed intracoronary imaging technique. In comparison with intravascular ultrasound, optical coherence tomography has a high resolution and offers microscopic visualization of coronary plaques. The authors clearly review the current literature and discuss the implications for clinical practice. The following paper is a clinical study by the same research group in which lesion characteristics detected by intravascular ultrasound were compared with images obtained with optical coherence tomography in 104 patients with unstable angina. This paper provides useful data because intracoronary imaging techniques are more and more used in daily practice.

The following three papers are all case reports. The first report is about two patients who both presented with stent fracture after everolimus-eluting stent implantation. Stent fracture has emerged as a potential mechanism of drug-eluting stent failure that is associated with in-stent restenosis. In the second case report, a patient is presented with an
anomalous left main coronary artery originating from right aortic sinus having retroaortic course that was complicated by a significant atherosclerotic narrowing. This patient was admitted with an acute coronary syndrome that was treated by percutaneous coronary intervention. In the last paper a case of acute thrombosis of two simultaneous coronary arteries in a young adult is described. The patient showed elevated homocysteine levels associated with homozygosity for the C677T gene mutation of methylenetetrahydrofolate reductase, a genetic condition that is associated with early coronary artery disease onset.

We hope that the readers will find this special issue of interest.

Alexander Hirsch
Robin Nijveldt
Igor Klem
Review Article

The Role of Cardiac Magnetic Resonance in the Evaluation of Patients Presenting with Suspected or Confirmed Acute Coronary Syndrome

Loren P. Budge¹ and Michael Salerno¹, ², ³

¹ Cardiology Division, Department of Medicine, University of Virginia Health System, 1215 Lee Street, P.O. Box 800158, Charlottesville, VA 22908, USA
² Department of Radiology, University of Virginia Health System, 1215 Lee Street, P.O. Box 800158, Charlottesville, VA 22908, USA
³ Department of Biomedical Engineering, University of Virginia Health System, 1215 Lee Street, P.O. Box 800158, Charlottesville, VA 22908, USA

Correspondence should be addressed to Michael Salerno, ms5pc@virginia.edu

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Cardiac magnetic resonance imaging (CMR) has an important emerging role in the evaluation and management of patients who present with symptoms concerning for acute coronary syndrome (ACS). This paper discusses the role of CMR in the emergency department setting, where CMR can aid in the early and accurate diagnosis of non-ST elevation ACS in low and intermediate risk patients. For those with confirmed myocardial infarction (MI), CMR provides comprehensive prognostic information and can readily diagnose structural complications related to MI. Furthermore, the pattern of late gadolinium enhancement (LGE) seen on CMR can help determine the etiology of cardiac injury in the subset of patients presenting with ACS who do not have obstructive coronary artery disease by angiography.

1. Introduction

Currently, more than a third of the 5.5 million people who present to the emergency department (ED) annually in the United States with a chief complaint of chest pain are admitted to the hospital, while only about a third of those admitted are eventually given the diagnosis of acute coronary syndrome (ACS) [1, 2]. Thus, the emergency department physician is confronted on a daily basis with patients who have symptoms worrisome for possible ACS. Available tools in the ED, which include a detailed medical history, physical exam, ECG, and serum cardiac biomarkers, have limitations for accurately and rapidly diagnosing ACS. Cardiac troponin I/T are quite sensitive for detecting myocardial injury, but often do not become elevated until hours after an infarction has occurred and may not be elevated in ACS without myocardial infarction. Triaging of these patients may be straightforward for high-risk patients, especially those with positive serum biomarkers (troponin I or T or myocardial fraction of creatine kinase) or with evidence of myocardial infarction (MI) on an electrocardiogram (ECG). However, for low- and intermediate-risk patients without immediate evidence of ischemia or MI on presentation, the decision of whether to admit can often be challenging. Furthermore, there is evidence that a small, but clinically significant number of patients are discharged from the ED with a missed diagnosis of ACS, including MI [3]. Missing the diagnosis of ACS and inappropriately discharging patients can result in adverse patient outcomes and is the leading cause of malpractice lawsuits and verdicts for physicians in the emergency room [4]. Because of the high prevalence and mortality associated with ACS, long observation times or admission to the hospital is often required. Even after patients have “ruled out” for MI, further functional or
anatomic testing is frequently performed for risk stratification. An ideal test for ACS in the ED would be able to quickly, accurately, and noninvasively triage patients with ACS symptoms shortly after arrival to the ED. Cardiac magnetic resonance imaging (CMR) is proving to be a powerful tool for the early identification or exclusion of ACS as the cause of a patient’s chest pain syndrome. Patients with evidence of MI on presentation to the ED often undergo an early invasive strategy consisting of cardiac catheterization with potential percutaneous coronary intervention (PCI). In this setting, CMR, performed after the intervention, has been shown to provide valuable prognostic information. Patients at low risk for ACS following CMR examination can potentially be discharged, thus reducing cost from unnecessary hospital admission. Additionally, for the challenging subset of patients with evidence of MI on presentation, but who have normal coronary arteries at catheterization, CMR is uniquely able to identify the correct etiology in the majority of cases. This paper will discuss the role of CMR in the early evaluation of patients presenting to the ED with symptoms concerning for ACS, the role of CMR after MI, and the role of CMR for assessing patients presenting with ACS who are found to have nonobstructive CAD by cardiac catheterization.

2. CMR Techniques for Evaluating ACS

CMR is capable of performing a rapid and comprehensive evaluation of cardiac anatomy, function, and myocardial perfusion at rest and/or during stress. CMR can accurately identify the presence of infarction, myocardial edema, microvascular obstruction, and intramyocardial hemorrhage. The sequence of a typical CMR exam for ACS usually begins with anatomic images of the chest, which can often provide clues about other pathologies that may be causing the patient’s chest pain. Cine steady-state free precession imaging provides an assessment of myocardial and valvular function and enables accurate assessment of left ventricular ejection fraction (LVEF) and ventricular volumes. CMR can assess myocardial edema and inflammation using T₂-weighted imaging due to the increased water content of the myocardium. Edematous tissues with higher water content have longer T₂ relaxation times, leading to a brighter signal on T₂-weighted images. First-pass myocardial perfusion is assessed using saturation-recovery gradient echo techniques during intravenous injection of gadolinium contrast agents. This can be performed during pharmacologic stress using adenosine or dobutamine infusion providing an assessment of myocardial ischemia. Myocardial scar is assessed by late gadolinium-enhanced (LGE) imaging, the pattern of which can help differentiate infarction from nonischemic processes. Regions with myocardial scar have a higher concentration of contrast agent and, thus, appear bright in these images. Conversely, areas of microvascular obstruction, thrombus, and myocardial hemorrhage appear dark on LGE imaging. A complete CMR protocol can be performed in less than 45 minutes providing a rapid comprehensive assessment of the heart.

3. Deciding Whether to Admit

CMR has been shown to improve both the diagnostic accuracy and time to diagnosis of ACS in the emergency department setting. This was demonstrated in a study of 161 patients presenting to the ED within 12 hours of onset of symptoms concerning for ACS, but without ST elevation on ECG [5]. The CMR exam in this study included cine MRI for LV function, resting first-pass perfusion, and LGE. Total CMR time was 38 minutes, and patients were gone from the ED for less than 1 hour. The sensitivity and specificity for diagnosis of ACS by CMR was 84% and 85%, respectively, and added independent diagnostic value to clinical parameters [5]. The main limitation of CMR in this study was its inability to differentiate acute from chronic MI, a problem which was addressed in a subsequent study by Cury et al., who added T₂-weighted imaging and LV wall thickness quantification to distinguish acute events [6]. T₂-weighted imaging enables visualization of edema associated with acute, but not chronic, myocardial infarction [7]. In this study, 62 patients with chest pain, normal ECG, and negative initial cardiac biomarkers, who were being admitted to the hospital to rule out MI, received CMR with an average scan time of 32 minutes. CMR with T₂-weighted imaging accurately identified all acute MI cases, often before cardiac biomarkers became elevated. Compared with conventional CMR, the addition of T₂-weighted edema imaging and wall thickness quantification increased specificity from 84% to 96%, positive predictive value from 55% to 85%, and overall accuracy from 84% to 93%; respectively, while sensitivity remained unchanged at 85% [6].

4. CMR without Initial Evidence of MI

A large proportion of low- and intermediate-risk patients presenting to the ED with symptoms concerning for ACS without evidence of MI undergo additional functional or anatomic imaging on either an inpatient or outpatient basis. CMR has been shown to compare favorably to other noninvasive cardiac imaging modalities for diagnosing ischemia. In a study by Nagel et al., 208 patients with suspected CAD underwent both dobutamine stress echo and dobutamine stress CMR prior to cardiac catheterization [8]. With CMR, sensitivity and specificity for detecting a 50% coronary stenosis was increased from 74.3% to 86.2% and from 69.8% to 85.7%, respectively, compared with echocardiography. In a study of 163 patients with poor acoustic windows preventing adequate imaging by dobutamine stress echo, Hundley et al. successfully performed dobutamine stress MRI in 153 of the patients [9]. The sensitivity and specificity for detecting a 50% coronary stenosis were 83% and 83%, respectively, in the 41 patients undergoing coronary angiography within 6 months of their stress test. In the 103 patients with negative stress tests, the event free survival at a median followup of 228 days was 97% [9]. A meta-analysis of dobutamine stress CMR including 14 studies (754 patients) with a high prevalence of coronary disease (prevalence: 70.5%) demonstrated a sensitivity of 83% and specificity of 86% [10]. Adenosine stress cardiac MRI has also been shown...
to be both sensitive and specific for detection of CAD. A meta-analysis including 1658 patients with intermediate likelihood of disease undergoing adenosine stress perfusion MRI demonstrated a sensitivity of 90% and specificity of 81%. The negative likelihood ratio of adenosine stress in this study was 0.14 [11]. A recent multicenter trial of 234 patients who were studied with both single photon emission computed tomography (SPECT) and CMR perfusion imaging demonstrated superior diagnostic utility for CMR perfusion at the ideal contrast dose as compared to SPECT [12]. In lower-risk populations presenting to the ED with chest pain, negative ECG, and negative serial cardiac biomarkers, CMR was performed in two separate studies evaluating a total of 192 patients who received adenosine stress and rest CMR, LV function assessment, and LGE [13, 14]. None of the patients with a normal CMR in either of these studies had any clinical events at 9-month followup. This was corroborated in a similar study of 135 low-risk patients presenting to the ED with chest pain who received adenosine stress CMR [15]. At 1 year followup, no patients with a normal stress CMR were found to have a significant coronary stenosis or cardiac event, yielding a sensitivity and specificity of 100% and 93%, respectively. Figure 1 shows an example of an adenosine stress CMR study in a diabetic patient presenting with new onset chest pain. Stress imaging demonstrates a large area of ischemia. This patient was found to have multivessel CAD.

The costeffectiveness of using stress CMR to evaluate intermediate- and high-risk patients in the ED setting was evaluated in a study of 110 patients with chest pain, negative ECG, and negative initial biomarkers, being admitted to the hospital to rule out MI [16]. These patients were randomized to obtain adenosine stress CMR while in the ED or usual inpatient care. All health care costs relating to their hospitalization and cardiac care over 30 days were included. There was no difference in 30-day outcomes between the groups. A diagnostic protocol which included stress CMR was found to reduce inpatient admissions and produced a cost savings of over 20% in this study [16]. Further cost-effectiveness studies are still needed to address the financial implications of utilizing stress CMR in lower-risk populations.

5. CMR following Myocardial Infarction

For those patients who present early after symptom onset with ST elevation MI (STEMI) or without ST elevation, but with elevated cardiac biomarkers (non ST elevation MI, or NSTEMI), an early invasive strategy with cardiac catheterization is generally recommended [17]. In these situations, it is usually not helpful to perform noninvasive cardiac testing prior to catheterization, because such tests could delay treatment and would not be expected to affect short-term patient management. CMR can be performed safely in MI patients, even immediately after percutaneous intervention [18, 19], add important prognostic information, diagnose post-MI complications, and aid in deciphering the etiology of cardiac injury in patients who present with STEMI, but who are found to have normal coronary arteries at catheterization. Figure 2 shows images from a patient who had a CMR study shortly after presenting with acute chest pain. In this case, edema imaging enabled appropriate determination of the LAD as the culprit vessel, even though there was no LGE in this region. The LGE in the lateral wall was from a prior myocardial infarction.

5.1. Prognosis. Left ventricular function has long been known to predict outcomes after MI. Impaired LV systolic function and an elevated LV end-systolic volume (ESV) are both powerful independent predictors of increased mortality [20–24]. CMR has become the gold standard for accurate quantification of left ventricular function and volumes. In contemporary CMR studies of post-MI patients, LVEF and LVESV are consistently predictive of outcomes; however, multiple studies have shown that other CMR-based parameters of infarction, such as infarct size, microvascular obstruction (MO), and myocardial salvage are more powerful predictors of outcomes than simple LV function or volume assessments [25–27].

5.2. Infarct Size. CMR-based assessment of infarct size using late gadolinium enhancement (LGE) is well validated and has been shown to be highly predictive of cardiac events at followup. Yokota et al. evaluated 86 patients with prior MI by CMR and found that infarct size by LGE was a better predictor of cardiac events than LVEF, LVESV or LVEDV, at 20 month follow up [27]. Cheong et al. followed a cohort of 857 patients with and without coronary artery disease for a median of 4.4 years and demonstrated that LGE, LVEF and heart failure symptoms were independent predictors of mortality [28]. Interestingly, patients with LGE and an ejection fraction more than 50% had the same outcomes as those with an LVEF less than 50% without LGE [28]. A study by Larose et al. investigated 103 acute ST elevation MI (STEMI) patients by CMR within 12 hours of
Figure 2: Determining acute from chronic infarcts. This patient had a CMR shortly after presenting with acute-onset chest pain. $T_2$-weighted imaging (a) reveals a bright signal in the mid-anteroseptum and apex, signifying edema, a marker of acute myocardial injury. Late gadolinium enhanced (LGE) imaging (b) shows an infarct in the mid-inferolateral wall, but minimal enhancement in the anteroseptum or apex. This patient had a severely stenosed mid-LAD as well as an occluded obtuse marginal branch of the circumflex coronary artery. CMR in this case was able to determine the culprit vessel.

PCI, after which they received a 6-month CMR and were followed for clinical events for an average of 2.4 years [29]. It was demonstrated that LGE measured immediately after revascularization strongly and independently predicted 6-month LVEF and long-term major cardiac events better than LVEF or clinical parameters. This was corroborated in a study of 122 STEMI patients who received CMR after revascularization and were followed for 2 years. Infarct size was again a stronger indicator of worsened LV function and clinical outcomes at followup than were baseline measurements of LV systolic performance [30].

5.3. Microvascular Obstruction. Microvascular obstruction (MO) refers to severe capillary and endothelial damage induced by prolonged ischemia, which prevents blood flow into the infarcted core after reperfusion. The extent of MO usually peaks between 2 hours to 2 days after reperfusion occurs [31–33], after which it tends to be stable in size until at least day 9 [34]. Thereafter areas of MO involute and regress and are rarely seen on followup CMR beyond 1 to 2 months after MI.

CMR has become the gold standard for assessment of MO, due to its excellent spatial resolution and tissue characterization ability. MO can be assessed by CMR using two separate techniques. Early MO is visualized early after contrast injection using first-pass perfusion. Typical protocols using this method define MO as hypoenhancement of the myocardium persisting longer than 1 to 2 minutes after initial contrast injection. The second technique collects late LGE images 10 to 15 minutes after contrast injection, and MO appears as an area or areas of hypoenhancement encompassed within a core of enhanced infarcted myocardium, often extending from the subendocardium. This latter method in the literature is sometimes termed persistent or late MO. Both methods of MO assessment have been validated, and there is not yet a clear consensus as to which method should be the preferred technique. Early MO has been shown to be predictive of long-term infarct size, infarct transmurality, LV function, and LV remodeling and is also a powerful independent long-term prognostic indicator of hard cardiac events even after controlling for infarct size [26, 35]; however, timing of the CMR examination after MI is important when assessing MO using first-pass perfusion. Early MO was more often seen when CMR was performed 2 days after MI than on days 7 or 9 but was not predictive of long-term functional or clinical outcomes until the later time points [34, 35]. Late MO has also been shown to lend additional prognostic information beyond that of infarct size or transmurality. In a study of 110 MI patients, Hombach et al. found that late MO independently portended an increase in cardiac events at 8-month followup and gave additional prognostic information compared to infarct size alone [36]. This was corroborated in a CMR study of 67 STEMI patients followed for 14 months, in which late MO was a better predictor of adverse cardiac events than infarct size or baseline ejection fraction [37]. Data comparing early and late MO are sparse, but, in a study by Nijveldt et al., 63 acute MI patients who received PCI and optimal medical management were followed by CMR with assessment of early, mid-, and late MO 4 to 7 days after MI and followup CMR at 4 months. In this study, late MO was a better predictor of follow up LV ejection fraction, LV end-diastolic volume, and LV end-systolic volume than early MO [38].

5.4. Area at Risk/Myocardial Salvage. The region of ischemic myocardium within the perfusion bed of an occluded coronary artery is the “area at risk” of infarction and is potentially salvageable with appropriate and timely intervention.
The area at risk, as measured by $T_2$-weighted CMR, correlates very well to the area at risk determined histologically with fluorescein staining [39]. Similarly, $T_2$-weighted in vivo CMR measurement of the area at risk 2 days following MI showed excellent correlation to the area at risk determined by fluorescent microspheres at the time of coronary occlusion [40].

Accurate assessment of both infarct size and the area at risk allows noninvasive measurement of a potentially clinically important parameter: the amount of myocardial salvage. The myocardial salvage index (MSI) is a measure of the myocardium that has been spared infarction, presumably due to a given procedure or treatment, and has important prognostic significance. CMR trials of STEMI patients undergoing PCI have repeatedly shown that an increase in the time from symptom onset to PCI leads to a significant incremental increase in infarct size and microvascular obstruction, with a corresponding decrease in myocardial salvage, while the extent of myocardial edema, or area at risk, remains unchanged [25, 41]. A trial of 208 STEMI patients who underwent PCI within 12 hours of symptom onset demonstrated that patients with an MSI above the study median experienced significantly fewer death, reinfarction, or heart failure events at 6 months when compared with those with an MSI below the median (2.9% versus 22.1%, $P < 0.001$) [25]. MSI was found to be a better predictor of outcome on multivariate regression than infarct size, MO, LVEF, TIMI flow-grade after PCI or ST segment resolution. Because of the unique ability of $T_2$-weighted CMR to detect myocardial salvage and predict adverse events, it may become an extremely valuable surrogate measure of outcome in studies of reperfusion therapy.

5.5. Right Ventricular Infarction. Another prognostic indicator after MI is the presence of right ventricular (RV) infarction. RV infarction has been associated with an increased risk of cardiogenic shock, atrioventricular conduction block, and rupture of the interventricular septum [42]. In-hospital mortality after RV infarction has been reported to be as high as 50% but, among survivors to hospital discharge, does not seem to predict long-term outcomes [43]. CMR has been demonstrated to be much more sensitive for detecting small or medium RV infarcts than physical exam, ECG with right-sided leads, or echocardiography [44, 45]. RV infarction, as seen by LGE of the RV after MI, was shown to be predictive of RV dilation at 6-month followup [46]. Furthermore, a recent CMR study of 50 MI patients undergoing successful PCI and followed for an average of 32 months reported RV involvement by LGE in 47% and 65% of inferior and anterior MIs; respectively, and found that RV infarction was a significant independent predictor of cardiac events (odds ratio: 15.8; 95% CI: 4–63), even after controlling for LV infarct size and location [45].

5.6. Postinfarct Complications. Due to CMR's unique tissue characterization abilities and spatial resolution, it is an ideal imaging modality for assessing complications arising after MI. CMR is widely considered the gold standard for analyzing both regional and global ventricular function after MI [47] and can comprehensively evaluate both systolic and diastolic function [48]. CMR can also readily detect ventricular wall pathology such as ventricular septal defects or free-wall aneurysms and can differentiate aneurysms from pseudoaneurysms, with its accompanying treatment implications. Visualization of LGE within the papillary muscles is indicative of infarction and has been reported in post-MI CMR studies to occur in 26 to 53% of patients [36, 49]. In a study of 60 patients with old MI, bilateral papillary muscle infarction was seen by LGE in 17% of cases and was associated with a higher incidence of severe mitral regurgitation and LV remodeling than in those with unilateral or no papillary muscle infarction [49]. Inflammatory pericarditis is visualized by LGE of the pericardium with high sensitivity and specificity after MI [50] and has been reported to occur in as many as 40% of STEMI patients [36]. CMR can also be beneficial in the evaluation of intraventricular thrombi. The presence of intraventricular thrombi has been reported in 7 to 29% of patients with decreased ejection fraction, depending on the population studied [51, 52], and is associated with a higher risk of thromboembolic events, including stroke [51, 53]. The most prominent risk factors for the development of LV thrombus include anterior infarction, infarct size, LV aneurysm, and decreased ejection fraction [52, 54]. A CMR protocol which includes LGE assessment has been shown to more accurately diagnose thrombi within the ventricle than transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE). In a multimodality imaging, study of 361 patients with ischemic cardiomyopathy undergoing cardiac surgery, the presence of LV thrombus by CMR, TTE, and TEE were compared to pathology and were found to have sensitivities and specificities of 88% and 99% for CMR, 23% and 96% for TTE, and 40% and 96% for TEE, respectively [51]. While contrast echocardiography nearly doubles the sensitivity of noncontrast echo, mural, and small apical LV thrombi are still frequently missed [55]. Recently, the use of prolonged inversion times (600 ms) during LGE imaging has been shown to increase the sensitivity of LGE for detecting thrombus even further [52]. Figure 3 shows images from a patient who presented late after an STEMI demonstrating a large area of LGE and the presence of an apical thrombus.

6. Myocardial Injury with Normal Coronary Arteries

An estimated 9–14% of patients who are diagnosed with STEMI will be found to have normal coronary arteries at cardiac catheterization [56]. These patients are at similar risk for mortality as those with CAD and often have an underlying pathology which can be difficult to diagnose. CMR is uniquely able to shed light on the underlying pathology in the majority of patients with MI with normal coronary arteries. The pattern of late gadolinium enhancement and myocardial edema in these patients is often helpful in differentiating the cause of injury. Ischemic necrosis begins in the subendocardium before extending to the epicardium; thus,
Figure 3: CMR imaging after acute MI. The tissue characterization abilities of CMR are demonstrated in these frames, all of which were taken from a patient who presented late after an ST elevation MI. A 4-chamber cine steady-state free precession (SSFP) image is shown in (a). Prior to contrast, it is difficult to discern whether there is thrombus in the apex. A postcontrast 4-chamber SSFP image (b) provides greater contrast between the slightly enhancing myocardium and nonenhancing thrombus at the apex. This difference is even more clear with late gadolinium-enhanced (LGE) imaging (c)-(d), which clearly demonstrates the black thrombus at the apex adjacent to the transmural apical infarct seen in white. An apical short axis view (d) reveals an extensive infarct with an area of microvascular obstruction visualized in the septum (arrow).

Figure 4: Myocardial infarction with normal coronary arteries. Images from a patient presenting with chest pain, elevated troponin but normal coronary arteries. Cine-SSFP images at (a) diastole and (b) systole demonstrate a wall motion abnormality in the inferoseptum and anterolateral walls. T2 weighted imaging (c) shows focal areas of edema in these regions. (d) LGE imaging demonstrates epicardial-delayed enhancement. These findings are consistent with the diagnosis of myocarditis.
sparing of the subendocardium in infarction is extremely rare. Conversely, subendocardial sparing is common in many nonischemic cardiomyopathies. Although myocarditis can present with varied LGE patterns, the classical appearance consists of a midwall or epicardial stripe of enhancement, the location of which can be indicative of the viral etiology [57, 58]. Figure 4 shows CMR images from a patient presenting with acute chest pain and a troponin elevation. Edema imaging indicated acute inflammation in the infereoseptum and anterolateral walls. LGE imaging shows epicardial scarring associated with myocarditis. Tako-Tsubo’s (stress-induced) cardiomyopathy, on the other hand, does not lead to scar formation or LGE. In a study of 1345 patients with diagnosed STEMI, 127 (9.5%) were found on angiography to have no coronary artery disease [59]. CMR in these patients had a 75% diagnostic yield and differentiated 31% as myocarditis, 31% as Tako-Tsubo cardiomyopathy, and 29% as STEMI without an angiographic lesion. This was corroborated in a study of 60 patients with troponin-positive chest pain, but unobstructed coronary arteries, which also found that CMR was able to provide a specific diagnosis in the majority of patients, diagnosing 50% of these cases as myocarditis and 11.6% as MI [60]. Myocardial edema, as seen with T2-weighted CMR, can help differentiate acute from chronic episodes of both ischemic and nonischemic events, and has been found to be present in acute episodes of Tako-Tsubo’s cardiomyopathy [61, 62], myocarditis [63], cardiac sarcoid [64], pulmonary hypertension [65], acute transplant rejection [66], and recent cardiac surgery.

### 7. Comparative Effectiveness of CMR in ACS

In the current era of cost awareness, there is an appropriate focus on the ability of an imaging modality to improve cost and real patient outcomes when compared with other available diagnostic strategies. As already discussed, there is a relatively large body of evidence demonstrating that CMR offers excellent diagnostic and prognostic data in ACS patients and that it compares favourably to other imaging modalities. It has also been found to be cost effective in a selected population of patients presenting to the ED with suspected ACS [16]. CMR can play a key role in appropriately determining which patients with chest pain need to be admitted for further management and which patients can be safely discharged to home; this could reduce costs related to unnecessary inpatient care. There is still a great need, however, for further studies to clarify CMR’s ability to directly change management, improve meaningful patient outcomes, and reduce overall costs of ACS care in the ED.

### 8. Conclusions

CMR has emerged as a robust diagnostic imaging modality capable of providing a comprehensive cardiac evaluation for patients with ACS. CMR is widely regarded as the reference standard for assessment of cardiac structure and function. In patients with acute myocardial infarction, CMR provides powerful diagnostic and prognostic information, allowing evaluation of cardiac function, infarct size and location, infarct complications, the extent of edema or area at risk, the amount of myocardial salvage, and the status of the microvasculature—all in a single scan. CMR has been shown to be safe, even immediately after PCI in STEMI patients [18, 19], and a comprehensive exam can typically be performed in less than 45 minutes without exposing the patient to radiation. For those with normal coronary arteries in the setting of MI, CMR provides clues to the underlying diagnosis in the majority of cases. For patients presenting to the emergency department with symptoms and risk factors concerning for ACS, but without evidence of MI, a comprehensive CMR study can also include stress perfusion imaging, allowing accurate functional assessment of the coronary circulation, which has been validated in both low and high risk study populations. T2-weighted imaging of edema and late gadolinium enhancement have the ability to detect infarction and severe ischemia early in the course of MI, even before cardiac biomarkers become elevated, and can differentiate acute from chronic infarction. Importantly, adding CMR to the emergency physician’s tool belt has been shown to improve diagnostic accuracy compared to current standards of care and to be cost effective in certain populations. Taken together, CMR provides a wealth of meaningful diagnostic and prognostic data for a wide range of patient populations with suspected or confirmed acute coronary syndrome.

### Abbreviations

- **ACS**: Acute coronary syndrome
- **CAD**: Coronary artery disease
- **CMR**: Cardiac magnetic resonance imaging
- **ECG**: Electrocardiogram
- **ED**: Emergency Department
- **HF**: Heart failure
- **LGE**: Late gadolinium enhancement
- **LV**: Left ventricle
- **LVEF**: Left ventricular ejection fraction
- **MI**: Myocardial infarction
- **NSTEMI**: Non-ST elevation myocardial infarction
- **PCI**: Percutaneous coronary intervention
- **RV**: Right ventricle
- **STEMI**: ST elevation myocardial infarction
- **UA**: Unstable angina.

### Disclosure

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### Funding

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Optical Coherence Tomography Imaging in Acute Coronary Syndromes

Takashi Kubo, Yasushi Ino, Takashi Tanimoto, Hironori Kitabata, Atsushi Tanaka, and Takashi Akasaka

Department of Cardiovascular Medicine, Wakayama Medical University, 811-1 Kimiidera, Wakayama 641-8510, Japan

Correspondence should be addressed to Takashi Kubo, takakubo@wakayama-med.ac.jp

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Optical coherence tomography (OCT) is a high-resolution imaging technique that offers microscopic visualization of coronary plaques. The clear and detailed images of OCT generate an intense interest in adopting this technique for both clinical and research purposes. Recent studies have shown that OCT is useful for the assessment of coronary atherosclerotic plaques, in particular the assessment of plaque rupture, erosion, and intracoronary thrombus in patients with acute coronary syndrome. In addition, OCT may enable identifying thin-cap fibroatheroma, the proliferation of vasa vasorum, and the distribution of macrophages surrounding vulnerable plaques. With its ability to view atherosclerotic lesions in vivo with such high resolution, OCT provides cardiologists with the tool they need to better understand the thrombosis-prone vulnerable plaques and acute coronary syndromes. This paper reviews the possibility of OCT for identification of vulnerable plaques in vivo.

1. Introduction

Optical coherence tomography (OCT) is a recently developed intravascular imaging modality using near-infrared light to create images [1–3]. The greatest advantage of OCT is its high resolution (10 to 20 μm), which is 10 times higher than that of intravascular ultrasound (IVUS). OCT can discriminate three layers of the coronary artery wall demonstrating the intima as the signal rich layer nearest the lumen, the media as the signal poor middle layer, and the adventitia as the signal rich layer surrounding the signal poor layer of the media [4]. With regard to tissue characterization, OCT allows us to identify three types of coronary plaques, such as fibrous, fibrocalcific, and lipid. Fibrous plaque is characterized by signal rich, homogenous lesion, fibrocalcific plaque by signal poor, sharp border lesion, and lipid rich plaques as signal poor, diffuse border lesion [5]. A histology-controlled OCT study showed good intra- and interobserver reliabilities (κ = 0.83–0.84) and high sensitivity and specificity in each plaque demonstrating 71–79% and 97–98% for fibrous plaques, 95–96% and 97% for fibrocalcific plaques, and 90–94% and 90–92% for lipid-rich plaques, respectively [5, 6]. Furthermore, OCT can detect plaque rupture (Figure 1), erosion (Figure 2), intracoronary thrombus (Figure 3), thin-cap fibroatheroma (TCFA; Figure 4), and calcified nodule (Figure 5) [7–9]. Although there are some limitations including shallow penetration depth of the infra-red light and complex procedure of image acquisition, the high resolution of OCT provides more detailed structural information of the coronary artery wall compared with conventional imaging modalities [10, 11]. Thus, OCT has been applied for the assessment of culprit lesion morphologies in patients with acute coronary syndrome (ACS).

2. Pathology of Culprit Lesions in ACS

Autopsy studies have demonstrated that ACS results from sudden luminal narrowing caused by thrombosis based on plaque rupture, erosion, and superficial calcified nodule [12, 13]. In these coronary features, plaque rupture is the most frequent (55 to 60%), plaque erosion to be the second (30 to 35%), and superficial calcified nodule to be the least (2 to 7%) [12]. Plaque rupture is identified by a presence of fibrous cap discontinuity and a cavity formation within the plaque. Atheroma with thin-fibrous
Plaque rupture. Plaque rupture is defined as a presence of fibrous-cap discontinuity (arrows) and a cavity formation (•) in the plaque. Ruptured plaques usually have an extensive lipid core and a thin fibrous cap. The fibrous cap is the thinnest at the site of rupture, and the plaque cavity indicates loss of lipid core due to rupture.

Plaque erosion. Erosion (arrowhead) is usually comprised of OCT evidence of thrombi (arrows), an irregular luminal surface, and no evidence of cap rupture evaluated in multiple adjacent frames. The characteristic of OCT features of erosions are a thick intima and a small or absent lipid core. If the lipid core is present, it does not communicate with luminal thrombi.

cap of <65 μm is thought to be precursor lesion of plaque rupture. Erosion has an area lacking surface endothelium and occurs over lesion with thick intima. Calcified nodule is a plaque with luminal thrombi showing calcific nodule protruding into the lumen through a disrupted thin fibrous cap. Based on these pathohistological findings, thrombosis-prone vulnerable plaques are characterized by 5 major and 5 minor features as listed in Table 1 [13]. Compared with conventional imaging modalities, OCT has an ability to identify these features more precisely in vivo.

Intracoronary thrombus. Thrombus is defined as a protrusion inside the lumen of the artery with signal attenuation. White thrombus which consists mainly of platelets is identified as signal rich, low-backscattering protrusions in the OCT image, while red thrombus which consists mainly of red blood cells is identified as high-backscattering protrusions inside the lumen of the artery, with signal-free shadowing in the OCT image.

Thin-cap fibroatheroma (TCFA). A fibrous cap (arrows) is identified as a signal-rich homogenous region overlying a lipid core (•), which is characterized by a signal-poor region. TCFA is defined as a plaque with a fibrous cap measuring <65 μm. OCT-detected TCFA s are often observed in the culprit lesions of acute coronary syndrome.

3. OCT Assessment of Culprit Lesions in ACS

The first OCT study to assess in vivo culprit lesion morphology in patients with ACS was conducted by Jang et al. [14]. They used a 3.2 Fr, proto-type OCT catheter and revealed higher frequency of TCFA in ACS compared with stable angina pectoris (SAP) (72% in acute myocardial infarction (AMI), 50% in unstable angina pectoris (UAP), and 20% in SAP; P = 0.012). However, this study showed lower frequency of thrombus and plaque rupture in AMI in
rupture site between exertion-triggered and rest-onset ACS. To compare the ruptured fibrous cap thickness and the onset and imaging (4 μm thick OCT catheter, the time delay between the symptom but it appears to be associated with healed plaques. The frequency of plaque rupture (73% versus 40% versus 43%, \( P = 0.021 \)) was observed more frequently in the UAP patients 9-month followup (28% versus 4%, \( P = 0.031 \)) was observed more frequently in the UAP patients compared with the SAP patients. At 9 months’ follow-up, the frequency of malapposed stent (33% versus 4%, \( P = 0.012 \)) and partially uncovered stent by neointima (72% versus 37%, \( P = 0.019 \)) was significantly greater in the UAP patients than that in the SAP patients. Recent OCT studies have suggested the development of in-stent neatherosclerosis after PCI. Kashiwagi et al. [20] compared with previous pathological reports [12, 13]. The thick OCT catheter, the time delay between the symptom onset and imaging (4.6 ± 5.3 days), and the thrombolysis and/or antiplatelet therapy before the imaging might affect the results. Thereafter, Kubo et al. [10] used commercially available OCT system with a 0.014 inch optic fiber, IVUS, and angioscopy in AMI within 6 hours from symptom onset. This study showed superiorities of OCT for the detection of plaque rupture (73% versus 40% versus 43%, \( P = 0.021 \)), erosion (23% versus 0% versus 3%, \( P = 0.003 \)), and thrombus (100% versus 33% versus 100%, \( P < 0.001 \)) compared with IVUS and angioscopy. The frequency of OCT-detected plaque rupture, erosion, and thrombus was similar to that of the pathological reports. The frequency of OCT-detected TCFA was 83%, and the thickness of fibrous cap was 49 ± 21 μm in AMI. Tanaka et al. [15] used OCT to compare the ruptured fibrous cap thickness and the rupture site between exertion-triggered and rest-onset ACS.

In the results, rest-onset ACS had thinner ruptured fibrous-cap thickness (50 μm versus 90 μm, \( P < 0.010 \)) and more frequent rupture near the shoulder of the plaque (57% versus 93%, \( P = 0.014 \)) in comparison with exertion-triggered ACS. Interestingly, not only TCFAs but also thick cap (up to 150 μm) fibroatheromas were ruptured in exertion-triggered ACS, and the high-sensitive C-reactive protein level was negatively correlated with the thickness of the ruptured fibrous-cap. Exercise-induced high shear stress at the site of the plaque shoulder and fibrous-cap inflammation might be associated with the fibrous-cap disruption of >65 μm thick. By using OCT, Ino et al. [16] showed differences of ruptured plaque morphologies between ST-segment elevated AMI and non-ST-segment elevated ACS. Although the minimum lumen area was similar in both groups, the ruptured cavity size was significantly larger in ST-segment elevated AMI compared with non-ST-segment elevated ACS. Furthermore, the ruptured plaque of which aperture was open wide against the direction of coronary flow was more often seen in ST-segment elevated AMI compared with non-ST-segment elevated ACS. The morphological feature of plaque rupture could relate to the clinical presentation in patients with ACS. Mizukoshi et al. [17] reported that the frequency of plaque rupture (43% versus 13% versus 71%, \( P < 0.001 \)) and plaque erosion (32% versus 7% versus 8%, \( P = 0.003 \)) was significantly different among the types of UAP; Braunwald class I, II, and III. The fibrous cap thickness (140 μm versus 150 μm versus 60 μm, \( P < 0.001 \)), minimal lumen area (0.70 mm² versus 1.80 mm² versus 2.31 mm², \( P < 0.001 \)), and the frequency of thrombus (72% versus 30% versus 73%, \( P < 0.001 \)) were also different among the types of UAP. This clinical OCT study disclosed that the culprit plaque in class III UAP might be more vulnerable than the other classes.

Unstable lesion morphologies before percutaneous coronary intervention (PCI) affect the outcome after the procedure. An observational OCT study [18] demonstrated that TCFAs was often seen at target lesions of the patients with noreflow after PCI compared with good reflow (50% versus 16%, \( P = 0.005 \)). The frequency of the noreflow phenomenon increased according to the size of the lipid arc as determined by OCT. A serial OCT study [19] showed markedly different vascular response up to 9 months after drug-eluting stent implantation between the patients with UAP and SAP. Acute stent malapposition (67% versus 32%, \( P = 0.038 \)) and tissue protrusion after PCI (79% versus 42%, \( P = 0.005 \)) were observed more frequently in the UAP patients. Plaque rupture was significantly increased after PCI in the UAP patients (42% to 75%, \( P = 0.018 \)), and the persistence of core cavity after plaque rupture at 9-month followup (28% versus 4%, \( P = 0.031 \)) was observed more frequently in the UAP patients compared with the SAP patients. At 9 months’ follow-up, the frequency of malapposed stent (33% versus 4%, \( P = 0.012 \)) and partially uncovered stent by neointima (72% versus 37%, \( P = 0.019 \)) was significantly greater in the UAP patients than that in the SAP patients.

Recent OCT studies have suggested the development of in-stent neatherosclerosis after PCI. Kashiwagi et al. [20]

**Table 1: Criteria for defining vulnerable plaques [13].**

<table>
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<tr>
<td>(1) Active inflammation (monocyte/macrophage and sometimes T-cell infiltration)</td>
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<tr>
<td>(2) Thin cap with large lipid core</td>
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<tr>
<td>(3) Endothelial denudation with superficial platelet aggregation</td>
</tr>
<tr>
<td>(4) Fissured plaque</td>
</tr>
<tr>
<td>(5) Stenosis &gt; 90%</td>
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</table>

<table>
<thead>
<tr>
<th>Minor criteria</th>
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<tbody>
<tr>
<td>(1) Superficial calcified nodule</td>
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<td>(2) Glistening yellow</td>
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<tr>
<td>(3) Intraplaque hemorrhage</td>
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<tr>
<td>(4) Endothelial dysfunction</td>
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<tr>
<td>(5) Outward (positive) remodeling</td>
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The mean cap thickness was 23 μm and was chosen as a criterion of instability because in rupture cavity formation (arrows). OCT disclosed a plaque rupture (arrowhead) and cavity formation (*) within neointima in the stented segment (arrows).

and Nishiguchi et al. [21] investigated the lesions with very late stent thrombosis by using OCT and demonstrated lipidic plaque formation, TCFA, and plaque rupture within the neointima in the stented segments. Although late stent thrombosis is thought to be associated with delayed endothelialization, these reports highlight that it can occur despite full stent coverage. Atherosclerotic developments within the neointima might play an important role in very late stent thrombosis (Figure 6).

4. OCT-Detected Vulnerable Plaques

The term “vulnerable plaque” is used to describe thrombosis-prone plaques. The precursor lesion for plaque rupture is characterized by a thin fibrous cap heavily infiltrated macrophages and an underlying lipid core. Virmani et al. [12] defined plaque vulnerability based on the actual thickness of the histological section from measurements made of plaque ruptures. TCFA was defined as a lesion with a fibrous cap <65 μm thick. A thickness of 65 μm was chosen as a criterion of instability because rupture of the mean cap thickness was 23 ± 19 μm; 95% of caps measured less than 65 μm within a limit of only two standard deviations. At present, OCT might be the best tool to detect TCFA in vivo [22–25]. Kume et al. [7] examined 35 lipid-rich plaques from 38 human cadavers and demonstrated a good correlation of the fibrous cap thickness between OCT and histology (r = 0.90; P < 0.001). In the clinical setting, Fujii et al. [26] showed that OCT-detected TCFA was associated with high-sensitive C-reactive protein, and its distribution in the coronary artery tree was similar to that in the previous autopsy reports. Kashiwagi et al. [27] used multidetector computed tomography to compare lesion characteristics between OCT-detected TCFA and non-TCFA. Positive remodeling (76% versus 31%, P < 0.001) and ring-like enhancement (44% versus 4%, P < 0.001) as determined by multidetector computed tomography were observed more frequently in OCT-detected TCFAs than in non-TCFAs. Computed tomography attenuation value was significantly lower in OCT-detected TCFAs than that in the non-TCFAs (35.1 ± 32.3 HU versus 62.0 ± 33.6 HU, P < 0.001). Kubo et al. [28] assessed the relationship between plaque color evaluated by coronary angioscopy and fibrous cap thickness estimated by OCT in vivo. As a result, there was a significant negative correlation between yellow color intensity and fibrous cap thickness (P < 0.001). Furthermore, 80% of intensive yellow plaques were OCT-detected TCFAs with a cap thickness of <65 μm. Sawada et al. [29] compared the feasibility for detecting TCFA between OCT and virtual histology IVUS. Although the positive ratio of virtual histology IVUS for detecting TCFA was 45.9%, that of OCT was 77.8%. On top of its reliability as a tool to measure the fibrous-cap thickness in vivo, a recent OCT study conducted by Takarada et al. [30, 31] demonstrated that the lipid-lowering therapy with statin for 9 months significantly increased the fibrous-cap thickness in patients with hypercholesterolemia (151 ± 110 to 280 ± 120 μm, P < 0.001). As therapies to prevent or make regression of atherosclerosis are developed, OCT can help to assess the treatment efficacy for plaque stabilization.

Plaque neovascularization is a common feature of vulnerable plaque. Proliferation of microvessels is considered to be related to intraplaque hemorrhage and plaque destabilization. The high resolution of OCT provides an opportunity to detect plaque neovascularization in vivo (Figure 7). Kitabata et al. [32] demonstrated increase of microvessels density in OCT-detected TCFAs in vivo. The presence of microvessels in the plaques was also associated with positive vessel remodeling and elevated high-sensitive C-reactive protein levels. The OCT evaluation of microvessels density might be helpful to assess plaque vulnerability.

A unique aspect of OCT is its ability to visualize the macrophages (Figure 8). Tearney et al. [33] and MacNeill et al. [34] described the potential of OCT to estimate macrophage accumulation within fibrous caps. There was a high degree of positive correlation between OCT and histological measurements of fibrous cap macrophage density (r < 0.84, P < 0.0001). A range of OCT signal deviation thresholds (6.15% to 6.35%) yielded 100% sensitivity and specificity for identifying caps containing >10% CD68 staining in their study.

5. Limitations of OCT

The current commercially available time-domain OCT system requires vessel occlusion by means of gentle balloon inflation and vessel flushing with lactated Ringers’ solution or saline infusion at the time of image acquisition because the near-infrared light signals are attenuated by red blood cells. Therefore, the assessment of long coronary segment and the observation of left main coronary artery might be limited. Inadequate displacement of blood can be a problem in vessels >3.5 mm in diameter, where large bifurcations are present and in the presence of competitive flow from collaterals or bypass grafts. In addition, there is concern about the local consequences of balloon inflation. To overcome
Figure 7: Plaque neovascularization. Microvessels within the intima (arrows) appear as signal poor voids that are sharply delineated. Two microvessels are located in thickened intima at 7 o'clock position. (\* = lipid).

Figure 8: Macrophages. Macrophages (arrows) are seen as signal-rich, distinct, or confluent punctuate regions that exceed the intensity of background speckle noise. The high contrast and resolution of OCT enable the quantification of macrophages within fibrous caps of atherosclerotic plaques.

This limitation, a simplified technique for coronary blood removal, which was achieved through continuous injection of contrast agents or dextran with lactate Ringers’ solution, is recommended [35, 36]. This nonocclusive technique of OCT image acquisition is safe and useful and promises to reduce the procedural time. A further limitation of OCT is the relatively shallow axial penetration depth of 2 mm. The OCT signal does not reach the back wall of thick atherosclerotic lesions. The penetration depth of OCT depends on tissue characteristics. Lipid-rich plaque or coronary thrombus causes OCT signal attenuation, which interrupts to observe deep layers of coronary artery wall. OCT is not appropriate for the quantification of lipid-core size and the evaluation of arterial remodeling. This drawback may affect the role of OCT for assessment of lesion instability. The current OCT is well suited for the assessment of the plaque morphologies within 500 \( \mu \)m of the luminal surface.

6. Future Perspectives of OCT

Recently, a second-generation OCT technology, named frequency-domain OCT, has been developed. This new technology will solve the current time-domain OCT limitations by imaging at much higher frame rates with slightly deeper penetration depth and greater scan area [37–39]. In combination with a short, nonocclusive flush and rapid spiral pullback, the higher frame rates generated by frequency-domain OCT enable imaging of the 3-dimensional microstructure of longer segments of coronary arteries [40]. In addition, frequency-domain OCT facilitates the acquisition of spectroscopic and polarization data for tissue characterization [41]. The development of frequency-domain OCT would allow easy and precise identification of vulnerable plaque in daily clinical practice.

7. Conclusions

The high resolution of OCT provides histology-grade definition of the microstructures of coronary unstable plaques in vivo. OCT can visualize unstable lesion morphologies in vivo which have been demonstrated by histological examinations. Thus, OCT allows a greater understanding of the pathophysiology of ACS and may have a potential to propose guidance for the appropriate patient-specific therapeutic approach. Although more clinical research with greater number of subjects and development of the imaging technology are required, OCT will play an important role in the future cardiology.

Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ACS</td>
<td>Acute coronary syndrome</td>
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<tr>
<td>AMI</td>
<td>Acute myocardial infarction</td>
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<tr>
<td>IVUS</td>
<td>Intravascular ultrasound</td>
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<tr>
<td>OCT</td>
<td>Optical coherence tomography</td>
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<tr>
<td>PCI</td>
<td>Percutaneous coronary intervention</td>
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<tr>
<td>SAP</td>
<td>Stable angina pectoris</td>
</tr>
<tr>
<td>TCFA</td>
<td>Thin cap fibroatheroma</td>
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<tr>
<td>UAP</td>
<td>Unstable angina pectoris</td>
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Disclosure

All authors do not have a financial interest, arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this paper.
References


Clinical Study

Optical Coherence Tomography Analysis of Attenuated Plaques Detected by Intravascular Ultrasound in Patients with Acute Coronary Syndromes

Takashi Kubo,1,2 Yoshiki Matsuo,1,2 Yasushi Ino,1 Takashi Tanimoto,1 Kohei Ishibashi,1 Kenichi Komukai,1 Hironori Kitabata,1 Atsushi Tanaka,1 Keizo Kimura,1 Toshio Imanishi,1 and Takashi Akasaka1

1 Department of Cardiovascular Medicine, Wakayama Medical University, 811-1, Kimiidera, Wakayama 641-8510, Japan
2 Department of Cardiovascular Medicine, Social Insurance Kinan Hospital, 46-70, Shinjyo-cho, Tanabe 646-8588, Japan

Correspondence should be addressed to Takashi Kubo, takakubo@wakayama-med.ac.jp

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1. Introduction

Intravascular ultrasound (IVUS) is widely used to evaluate vulnerable plaques in patients with coronary artery disease. Attenuated plaque, which is defined as a hypoechoic plaque with deep ultrasound attenuation despite absence of bright calcium, is more often observed in patients with acute coronary syndrome than in those with stable angina [1]. Recent IVUS studies have shown that attenuated plaque is associated with a higher C-reactive protein level, more severe and complex lesion morphology, reduced coronary blood flow before percutaneous coronary intervention, and especially no-reflow after the procedure [2]. However, histopathologic characteristics of attenuated plaque have not been fully investigated. Optical coherence tomography (OCT) is an optical analogue of IVUS that provides high-resolution (10–20 μm) cross-sectional images of coronary arteries. The micron-scale resolution of OCT allows excellent differentiation of atherosclerotic plaque components such as fibrous, fibrocalcific, and lipid [3, 4]. Moreover, OCT can identify vulnerable plaque features including plaque rupture, thrombus, and thin-cap fibroatheroma (TCFA) [5, 6]. Therefore, we used OCT to compare lesion characteristics between IVUS-detected attenuated plaque and nonattenuated plaque.

2. Materials and Methods

2.1. Study Population. A total of 104 patients with primary unstable angina pectoris (UAP) who had de novo coronary lesions and underwent OCT and IVUS to evaluate culprit lesion morphologies in Wakayama Medical University, Wakayama, Japan, and Social Insurance Kinan Hospital, Wakayama, Japan, were studied retrospectively. UAP was defined according to the Braunwald clinical classification [7, 8]: class I, new onset of severe angina or accelerated...
angina, no pain at rest; class II, angina at rest within previous month but not within preceding 48 hours; class III, angina at rest within 48 hours. Patients with secondary UAP and postinfarction angina were not included. Patient hospital records were reviewed to obtain information on clinical demographic data and medical history. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or use of antihypertensive drugs. Hypercholesterolemia was defined as a present or past history of low-density lipoprotein-cholesterol level ≥140 mg/dl, or use of statin. Diabetes mellitus was defined as a fasting blood sugar ≥126 mg/dl and haemoglobin A1c ≥6.5%, or use of antidiabetic medications (insulin or oral hypoglycaemics). This study was approved by the institutional review boards of the institutions in which the procedures were performed, and all patients gave written informed consent before cardiac catheterization.

2.2. OCT Imaging and Analysis. OCT (the M2 OCT imaging system, LightLab Imaging, Inc, Westford, Mass, USA) was performed before any intervention and IVUS imaging. We used a continuous-flushing (nonocclusive) method for OCT image acquisition. A 0.016-inch wire-type imaging catheter was positioned distal to the culprit lesion. To remove blood cells from the field of view, a mixture of commercially available dextran 40 and lactated Ringer solution was infused from the guiding catheter at 2.5 to 4.5 mL/s with an injector pump. The culprit lesion was imaged with a motorized pull-back device travelling at 1 mm/s. Continuous OCT images were stored digitally for subsequent analysis. The OCT analysis was performed by 2 independent observers who were blinded to the IVUS findings. When there was any discordance between the observers, a consensus reading was obtained. IVUS-OCT findings. When there was any discordance between the observers, a consensus reading was obtained. IVUS-OCT findings. When there was any discordance between the observers, a consensus reading was obtained. IVUS-OCT findings. When there was any discordance between the observers, a consensus reading was obtained. IVUS-OCT findings. When there was any discordance between the observers, a consensus reading was obtained. IVUS-OCT findings. When there was any discordance between the observers, a consensus reading was obtained. IVUS-OCT findings. When there was any discordance between the observers, a consensus reading was obtained. IVUS-OCT findings. When there was any discordance between the observers, a consensus reading was obtained. IVUS-OCT findings. When there was any discordance between the observers, a consensus reading was obtained. IVUS-OCT findings. When there was any discordance between the observers, a consensus reading was obtained. IVUS-OCT findings. When there was any discordance between the observers, a consensus reading was obtained. IVUS-OCT findings. When there was any discordance between the observers, a consensus reading was obtained. IVUS-OCT findings. When there was any discordance between the observers, a consensus reading was obtained. IVUS-OCT findings. When there was any discordance between the observers, a consensus reading was obtained. IVUS-OCT findings. When there was any discordance between the observers, a consensus reading was obtained. IVUS-OCT findings. When there was any discordance between the observers, a consensus reading was obtained.

2.3. IVUS Imaging and Analysis. After intracoronary administration of nitroglycerin (0.2 mg), the IVUS examination was performed using a commercial scanner (Boston Scientific Corporation, Maple Grove, Minn, USA) that consisted of a 40-MHz transducer. The IVUS catheter was advanced beyond the culprit lesion followed by automatic transducer pull back (at 0.5 mm/s) to the aorto-ostial junction. IVUS images were recorded onto a DVD for offline analysis. Using custom-built software, IVUS images were analyzed by 2 independent observers who were blinded to the OCT findings. When there was any discordance between the observers, a consensus reading was obtained. IVUS-detected attenuated plaque was defined as a hypoechoic plaque with deep ultrasound attenuation despite absence of bright calcium [1, 2]. Representative images are shown in Figure 1. To obtain corresponding images of IVUS and OCT, the distances from at least 2 landmarks, such as side branches and/or calcifications, were referred. Quantitative IVUS measurements included external elastic membrane (EEM), lumen, and plaque and media (P&M: defined as EEM minus lumen) cross-sectional area, and plaque burden (defined as P&M divided by EEM) [9]. If the EEM circumference could not be identified because of attenuation, we interpolated the EEM area [2, 11]. The lesion site was defined as the slice with the minimum lumen area. The proximal and distal reference sites were defined as the slices with the most normal looking segments (largest lumen with least plaque) >5 mm proximal and distal to the lesion, but before a major side branch. The remodeling index was calculated as the lesion EEM divided by the mean reference EEM. Positive remodeling was defined as a remodeling index >1.05 [10].

2.4. Angiographic Analysis. Quantitative coronary angiography analysis was performed using the Cardiovascular Measurement System (CMS, Medis Medical Imaging System, Leiden, The Netherlands). Angiographic lesion morphology was classified according to the ACC/AHA classification [12]. The percentage of diameter stenosis was measured in the view that was the most severe and not foreshortened.

2.5. Statistical Analysis. Statistical analysis was performed using Statview 5.0.1 (SAS Institute, Cary, NC, USA). Categorical variables were presented as absolute numbers and percentages, with comparison using chi square statistics or Fisher exact test, if there was an expected cell value <5. Continuous variables were presented as mean ± standard deviation and were compared using Student’s t-test. All analyses required a P < 0.05 for statistical significance.

3. Results

IVUS-detected attenuated plaque was observed in 41 (39%) patients with UAP. Clinical and angiographic characteristics are listed in Table 1. There were no significant differences in coronary risk factors between the patients with attenuated and nonattenuated plaque. Although the frequency of Braunwald clinical class I (20% versus 49%, P = 0.002) and class II (7% versus 29%, P = 0.011) was significantly lower in the attenuated plaque group compared with the nonattenuated plaque group, the frequency of class III (73% versus 22%, P < 0.001) was significantly higher in the attenuated plaque group. Angiographic lesion characteristics were similar between the 2 groups.

IVUS findings are summarized in Table 2. Minimum lumen area (2.5 ± 1.0 mm² versus 2.6 ± 1.0 mm², P = 0.676)
Figure 1: IVUS images of attenuated plaques and corresponding OCT images. OCT revealed that IVUS-detected attenuated plaques include (a) lipidic plaque with fibrous cap of 380 μm thick and lipid arc of 130 degree, (b) thin-cap fibroatheroma with fibrous cap of 60 μm thick and lipid arc of 160 degree, (c) plaque rupture (*), and (d) mural thrombi (arrows).
Table 1: Clinical and angiographic characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Attenuated plaque (n = 41)</th>
<th>Nonattenuated plaque (n = 63)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>75 ± 7</td>
<td>73 ± 7</td>
<td>0.169</td>
</tr>
<tr>
<td>Male</td>
<td>28 (68)</td>
<td>42 (67)</td>
<td>0.863</td>
</tr>
<tr>
<td>Hypertension</td>
<td>33 (80)</td>
<td>44 (70)</td>
<td>0.226</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>11 (27)</td>
<td>19 (30)</td>
<td>0.714</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>24 (59)</td>
<td>36 (57)</td>
<td>0.888</td>
</tr>
<tr>
<td>Current smoker</td>
<td>15 (37)</td>
<td>15 (24)</td>
<td>0.160</td>
</tr>
<tr>
<td>Braunwald clinical classification of UAP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>8 (20)</td>
<td>31 (49)</td>
<td>0.002</td>
</tr>
<tr>
<td>Class II</td>
<td>3 (7)</td>
<td>18 (29)</td>
<td>0.011</td>
</tr>
<tr>
<td>Class III</td>
<td>30 (73)</td>
<td>14 (22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Culprit vessel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>14 (34)</td>
<td>19 (30)</td>
<td>0.669</td>
</tr>
<tr>
<td>LCX</td>
<td>7 (17)</td>
<td>8 (13)</td>
<td>0.535</td>
</tr>
<tr>
<td>RCA</td>
<td>20 (49)</td>
<td>36 (57)</td>
<td>0.403</td>
</tr>
<tr>
<td>ACC/AHA lesion classification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type A</td>
<td>8 (20)</td>
<td>18 (29)</td>
<td>0.297</td>
</tr>
<tr>
<td>Type B1</td>
<td>17 (41)</td>
<td>24 (38)</td>
<td>0.731</td>
</tr>
<tr>
<td>Type B2</td>
<td>11 (27)</td>
<td>13 (21)</td>
<td>0.464</td>
</tr>
<tr>
<td>Type C</td>
<td>5 (12)</td>
<td>8 (13)</td>
<td>0.940</td>
</tr>
<tr>
<td>Diameter stenosis, %</td>
<td>85 ± 7</td>
<td>83 ± 7</td>
<td>0.178</td>
</tr>
</tbody>
</table>

Values are given as n (%) or mean ± standard deviation. UAP: unstable angina pectoris; LAD: left anterior descending coronary artery; LCX: left circumflex coronary artery; RCA: right coronary artery.

Table 2: Intravascular ultrasound findings.

<table>
<thead>
<tr>
<th></th>
<th>Attenuated plaque (n = 41)</th>
<th>Nonattenuated plaque (n = 63)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum lumen area site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EEM area, mm²</td>
<td>12.4 ± 5.0</td>
<td>10.1 ± 4.4</td>
<td>0.016</td>
</tr>
<tr>
<td>Lumen area, mm²</td>
<td>2.5 ± 1.0</td>
<td>2.6 ± 1.0</td>
<td>0.676</td>
</tr>
<tr>
<td>P&amp;M CSA, mm²</td>
<td>9.9 ± 4.6</td>
<td>7.5 ± 4.0</td>
<td>0.006</td>
</tr>
<tr>
<td>Plaque burden, %</td>
<td>78 ± 10</td>
<td>73 ± 9</td>
<td>0.022</td>
</tr>
<tr>
<td>Positive remodeling, %</td>
<td>22 (54)</td>
<td>19 (30)</td>
<td>0.017</td>
</tr>
<tr>
<td>Proximal reference site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EEM area, mm²</td>
<td>12.5 ± 5.3</td>
<td>10.9 ± 4.4</td>
<td>0.112</td>
</tr>
<tr>
<td>Lumen area, mm²</td>
<td>8.6 ± 3.7</td>
<td>7.4 ± 3.3</td>
<td>0.117</td>
</tr>
<tr>
<td>P&amp;M area, mm²</td>
<td>3.9 ± 1.9</td>
<td>3.5 ± 1.3</td>
<td>0.170</td>
</tr>
<tr>
<td>Plaque burden, %</td>
<td>31 ± 6</td>
<td>32 ± 6</td>
<td>0.500</td>
</tr>
<tr>
<td>Distal reference site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EEM area, mm²</td>
<td>11.4 ± 5.4</td>
<td>9.9 ± 4.4</td>
<td>0.123</td>
</tr>
<tr>
<td>Lumen area, mm²</td>
<td>8.1 ± 3.8</td>
<td>7.0 ± 3.3</td>
<td>0.133</td>
</tr>
<tr>
<td>P&amp;M CSA, mm²</td>
<td>3.4 ± 1.7</td>
<td>2.9 ± 1.3</td>
<td>0.144</td>
</tr>
<tr>
<td>Plaque burden, %</td>
<td>29 ± 5</td>
<td>29 ± 5</td>
<td>0.974</td>
</tr>
</tbody>
</table>

Values are given as mean ± standard deviation. EEM: external elastic membrane; CSA: cross-sectional area; P&M: plaque and media.

was similar between attenuated plaques and nonattenuated plaques. At the minimum lumen area site, EEM area (12.4 ± 5.0 mm² versus 10.1 ± 4.4 mm², $P = 0.016$), P&M area (9.9 ± 4.6 mm² versus 7.5 ± 4.0 mm², $P = 0.006$), plaque burden (78 ± 10% versus 73 ± 9%, $P = 0.022$), and frequency of positive remodeling (54% versus 30%, $P = 0.017$) were significantly greater in attenuated plaques compared with nonattenuated plaques.

OCT findings are summarized in Table 3. The frequency of lipidic plaque (88% versus 49%, $P < 0.001$) was
significantly higher in attenuated plaques compared with nonattenuated plaques, while the frequency of fibrocalcific plaque (12% versus 42%, P = 0.002) and fibrotic plaque (0% versus 9%, P = 0.042) was significantly lower in attenuated plaques. In the lipidic plaques, fibrous cap thickness (103 ± 70 μm versus 145 ± 97 μm, P = 0.040; Figure 2) was significantly thinner and lipid arc (204 ± 57 degree versus 166 ± 48 degree, P = 0.004; Figure 3) was significantly greater in attenuated plaques compared with nonattenuated plaques. OCT-detected TCFA (48% versus 16%, P < 0.001), plaque rupture (44% versus 11%, P < 0.001), and intracoronary thrombus (54% versus 17%, P < 0.001) were more often seen in attenuated plaques compared with nonattenuated plaques.

4. Discussion

In this IVUS and OCT study, we demonstrated that IVUS-detected attenuated plaques are associated with lipidic plaque, TCFA, plaque rupture, and intracoronary thrombus. Our results suggest the biologic instability of these lesions.

IVUS is a useful tool for identification of high-risk or unstable lesion morphologies. Previous IVUS data have indicated that culprit lesions in acute coronary syndromes often have a large plaque burden [13, 14], positive remodeling [15, 16], hypoechoic (soft) plaque [17, 18], lipid pool-like plaque characteristics [19, 20], and attenuated plaque [1, 2]. Lee et al. demonstrated that attenuated plaques were more common in patients with ST-segment elevation myocardial infarction than in those with non-ST-segment elevation myocardial infarction (40% versus 18%, P < 0.001) and were associated with a higher C-reactive protein level and more complex lesion morphology on angiography [2]. In their study, the location of attenuated plaques was similar to the location of acute occlusions or plaque ruptures, especially with regard to proximal distribution in the left anterior descending coronary artery and right coronary artery [2]. Okura et al. showed that attenuated plaques are related with no reflow and creatine kinase-MB elevation after percutaneous coronary intervention because of distal embolization [1]. Although there is an IVUS study showing attenuated plaques in stable patients [11], most studies support the hypothesis that attenuated plaque is a part of the unstable lesion morphometric spectrum.

OCT has an excellent ability for coronary plaque characterization and vulnerable plaque detection. Histological validation of OCT revealed good intra- and interobserver reliability (κ = 0.83–0.84) as well as excellent sensitivity and specificity: 71–79% and 97–98% for fibrous plaques; 95–96% and 97% for fibrocalcific plaques; 90–94% and 90–92% for lipid-rich plaques, respectively [3]. A multimodality imaging study in acute myocardial infarction disclosed superiority of OCT for detection of plaque rupture (73% versus 40% versus 43%, P = 0.021) and intracoronary thrombus (100% versus 33% versus 100%, P < 0.001) [5]. Moreover, OCT might be the best tool available to detect TCFA in vivo because a good correlation was seen for the measurements of the fibrous cap thickness between OCT and histological examination (r = 0.90; P < 0.001) [6]. Therefore, we used OCT to evaluate lesion characteristics and demonstrated that IVUS-detected attenuated plaques were associated with lipidic plaque, TCFA, plaque rupture, and intracoronary thrombus. Our results could contribute to the understanding of attenuated plaque and its potential relationship to plaque vulnerability.

Recent studies have shown the mechanisms of ultrasound attenuation in atherosclerotic plaques. In human cadaver coronary arteries, Yamada et al. demonstrated that the per-centange of necrotic core area was significantly greater in attenuated plaques than nonattenuated plaques [21]. In line with this histologic study, Wu et al. confirmed
Table 3: Optical coherence tomography findings.

<table>
<thead>
<tr>
<th>Lesion type</th>
<th>Attenuated plaque (n = 41)</th>
<th>Nonattenuated plaque (n = 63)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipidic</td>
<td>36 (88)</td>
<td>31 (49)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fibrocalcific</td>
<td>5 (12)</td>
<td>26 (42)</td>
<td>0.002</td>
</tr>
<tr>
<td>Fibrotic</td>
<td>0 (0)</td>
<td>6 (9)</td>
<td>0.042</td>
</tr>
<tr>
<td>TCFA</td>
<td>20 (48)</td>
<td>10 (16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Plaque rupture</td>
<td>18 (44)</td>
<td>7 (11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thrombus</td>
<td>22 (54)</td>
<td>11 (17)</td>
<td></td>
</tr>
</tbody>
</table>

Values are given as n (%). TCFA: thin-cap fibroatheroma.

in vivo that attenuated plaques were associated with a large amount of necrotic core as determined by virtual histology IVUS imaging [22]. Ito et al. examined directly coronary atherectomy specimens from attenuated plaques and found mature atherosclerosis consisting predominantly of hyalinization, scattered, small areas of calcification, and cholesterol clefts [23]. The random distribution of microcalcification and cholesterol crystals within lipid-rich necrotic core is thought to be responsible for ultrasound wave reflection and dispersion and, as a result, attenuation within the IVUS image [24]. In addition, an animal model has suggested that thrombi with abundant cellular elements could cause backward attenuation due to ultrasound dispersion [25]. The present study showed higher frequency of lipidic plaque and intracoronary thrombus in attenuated plaques compared with nonattenuated plaques. Our result supports the hypothesis that lipid-rich necrotic core of the mature atherosclerotic plaque and intracoronary thrombus maybe important mechanisms of ultrasound attenuation.

5. Limitations

There were several limitations. First, this was a retrospective study in nonconsecutive UAP patient. Therefore, the prevalence, clinical feature, and prognostic implication of IVUS-detected attenuated plaque need to be examined by a larger population study. Second, we only included UAP patients. In the examination of attenuated plaque and its potential relationship to plaque vulnerability, our study is limited by the lack of a comparison group with stable presentation. Third, in the IVUS analysis, acoustic shadowing in attenuated plaques may interfere with calculation of remodeling and plaque burden. Fourth, in the OCT analysis, signal attenuation of lipidic tissue or thrombus may preclude visualization and measurement of the entire atherosclerotic plaque. Finally, we used 40-MHz IVUS transducers according to the most previous studies of attenuated plaques. Our results may be not applicable for the IVUS images acquired by other frequency transducers, because the IVUS frequency can affect the degrees of signal penetration (e.g., 20-MHz transducers utilized in virtual histology IVUS have greater penetration than 40-MHz transducers).

6. Conclusions

IVUS-detected attenuated plaque has many characteristics of unstable coronary lesion. The presence of attended plaque might be an important marker of lesion instability.

Abbreviations

EEM: External elastic membrane
IVUS: Intravascular ultrasound
OCT: Optical coherence tomography
P&M: Plaque and media
TCFA: Thin-capped fibroatheroma
UAP: Unstable angina pectoris.

Disclosure

All authors do not have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interests in the context of the subject of this paper.

References


Case Report
Stent Fracture after Everolimus-Eluting Stent Implantation

Ali S. Almasood, Xavier Freixa, Sohail Q. Khan, Peter H. Seidelin, and Vladimír Džavík

Interventional Cardiology Program, Division of Cardiology, Peter Munk Cardiac Centre, University Health Network, University of Toronto, 6-246 EN, Toronto General Hospital, 200 Elizabeth Street, Toronto, ON, Canada M5G 2C4

Correspondence should be addressed to Vladimír Džavík, vlad.dzavik@uhn.on.ca

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Compared with bare-metal stents, drug-eluting stents (DES) have greatly reduced the risk of in-stent restenosis (ISR) by inhibiting neointimal growth. Nevertheless, DES are still prone to device failure, which may lead to cardiac events. Recently, stent fracture (SF) has emerged as a potential mechanism of DES failure that is associated with ISR. Stent fracture is strongly related to stent type, and prior reports suggest that deployment of sirolimus eluting stents (SES) may be associated with a higher risk of SF compared to other DES. Everolimus eluting stents (EESs) represent a new generation of DES with promising results. The occurrence of SF with EES has not been well established. The present paper describes two cases of EES fracture associated with ISR.

1. Introduction

The occurrence of stent fractures (SF) is recognized as a potential complication of stent deployment. Its incidence varies markedly in published reports, ranging from less than 1% to more than 16% [1–3]. Little is known about the precise incidence of SF in the “real world”. However, SF is likely to be underrecognized due to difficulty in diagnosis and the lack of standardized definitions. Stent fracture has currently become an important concern after drug-eluting stent (DES) implantation due to its potential association with in-stent restenosis (ISR) and stent thrombosis [4]. Sirolimus-eluting stents (SES), as compared with paclitaxel (PES) or zotarolimus-eluting stents (ZES), are considered the DES with the highest risk of SF [5, 6].

The everolimus eluting stent (EES; Multilink Vision platform, Abbott Vascular, Temecula, CA), is a new DES with promising long-term results [7–9]. As compared with other DES, EES provides the thinnest available strut profile (0.08 mm) [10]. The incidence of SF with EES has never been assessed. The present paper describes two cases of EES fracture associated with ISR.

2. Case Reports

2.1. Case-1. This patient was a 72-year-old lady with a chief complaint of prolonged chest pain. Her medical history included hypertension, hyperlipidemia, family history of coronary artery disease, and cutaneous lupus erythematosus. In May 2009, she experienced exertional chest pain and underwent coronary angiography which revealed a calcific 90% mid- and 80% distal RCA stenosis. The distal lesion was treated with rotational atherectomy using 1.25 mm burr following which a 2.25 × 23 mm Xience V stent (Abbott Vascular Devices, Santa Clara, CA) was deployed at 16 atmospheres (ATM). A 2.75 × 28 mm Xience V stent was then deployed at 16 ATM in the mid-segment, and postdilated with a 3.25 × 10 mm noncompliant balloon up to 24 ATM. An excellent result was achieved, and she was discharged home in a stable condition (Figure 1). Four months later she presented to the emergency department with a prolonged episode of chest pain associated with T wave inversion in the inferior leads and an elevated troponin I. Coronary angiography revealed focal in-stent restenosis (ISR) in the mid-RCA (Figure 2(a)). Multiple fluoroscopic
images revealed a gap in the middle of the EES stent indicating a complete stent fracture (Figure 2(b)) probably related to the severe calcification and angulation of the artery. We elected to cover this with a further stent. Predilation was performed with a 2.5 × 15 mm balloon at 18 ATM and a 3.0 × 13 mm Cypher Select Plus stent was delivered at 24 ATM, with an excellent final result. No further angiograms were performed as the patient remained free of symptoms.

2.2. Case-2. This patient was a 67-year-old lady with recurrent chest pain associated with dyspnea. Her medical history included former smoking, hypertension, hyperlipidemia, diabetes mellitus, and chronic obstructive pulmonary disease. She underwent quadruple bypass surgery in 2004 with a left internal thoracic artery (LITA) to the LAD and 3 venous grafts, to the RCA, diagonal, and obtuse marginal arteries. She required a dual-chamber pacemaker 2 days after bypass surgery. In July 2005, she developed stable class III angina, and coronary angiography revealed a stenosis where the LITA was inserted into the LAD. This was treated with a bare metal stent (BMS). She was stable until June 2009 when she developed recurrent angina and was found to have ISR within the BMS stent. On this occasion, we elected to perform PCI and stenting of the native LAD across the distal anastomosis of the LITA graft. A total of three overlapping everolimus eluting stents (EESs) were deployed. A 2.5 × 18 mm and 2.5 × 25 mm Xience V stents and 2.25 × 15 mm Promus stent (Boston Scientific Corp., Natick, MA) were implanted from distal to proximal with good angiographic results (Figure 3). Five months later, she again presented with progressive angina. Repeat coronary angiography demonstrated focal in-stent restenosis in two stents (the 2.5 × 18 mm Xience V and the 2.25 × 15 mm Promus). Further angiographic evaluation revealed stent strut separation in the two stents at the focal ISR site indicating a complete stent fracture (Figure 4). Predilatation of both sites was performed with a 2.5 × 15 mm balloon. We deployed a 2.5 × 14 mm Endeavor stent (Medtronic CardioVascular, Santa Rosa, CA) covering the distal stent fracture position at 18 ATM. Considerable stent movement was visible with each cardiac cycle. We felt that additional stenting and structural support would be required for success. Therefore a second Endeavor 3.0 × 30 mm stent was deployed to cover this segment, extending back through
the ISR in the mid-LAD. The mid-portion of the stented segment was then postdilated with a 3.0 × 15 mm noncompliant balloon to a maximum of 22 ATM. An excellent angiographic result was obtained (Figure 5). Subsequently, she presented in July 2009 again with troponin-negative progressive angina. Repeat coronary angiography revealed that she had a fracture within her Endeavor 3.0 × 30 mm stent (Figure 6) and had developed occlusive ISR within her LAD. On this occasion, she had repeat PCI to her LITA into LAD with further deployment of an Endeavor 2.5 × 30 mm with a good angiographic result.

3. Discussion

Stent fracture, currently an important concern after DES implantation, has been associated with a higher potential risk of ISR and stent thrombosis [4]. The mechanism of ISR in stent fracture is probably related to lower drug delivery at the fracture site and higher mechanical irritation by the fractured struts causing smooth muscle proliferation and impaired reendothelization [11]. Stent fracture has been linked to longer stent length, stent overlap, stent overexpansion, lesion calcification, severe angulation and dynamic flexure [5, 12, 13]. Sirolimus-eluting stent deployment is also considered a risk factor for SF [5, 6]. Nonetheless, it remains unclear if the relatively high incidence of SF is related to its strut structure, component materials, the type of antiproliferative drug, or just because it is underdetected as compared with other stents [6].

The risk of SF in EES has never been assessed, perhaps due to the relatively new introduction of this stent. EES uses cobalt chromium technology and confers a very unique architecture with the thinnest strut profile [10]. It remains unknown if this design and the cobalt chromium composition might modify the risk of SF compared to the stainless steel DES generation (SES and PES). In our case reports, SF was associated with a focal ISR pattern, which is very frequently seen with SES fractures [14]. The fracture sites were all at hinge movement points that occur in areas of curves and twists leading to increased shear forces on the vessel wall and stent. The repetitive cardiac contractions may ultimately lead to metal fatigue and fracture. Both patients
Figure 5: Angiographic images of the left anterior descending artery after two Endeavor stents deployment showing the absence of stent strut separation (a) and the presence of a good angiographic result (b).

Figure 6: Complete Endeavor stent fracture of the distal left anterior descending coronary artery.

presented with an acute coronary syndrome secondary to ISR without evidence of stent thrombosis.

The treatment of SF is a challenging situation due to the absence of formal recommendations. In our cases, we used a different stent platform and polymer coating to treat the stent fractures. In the first case, we used an SES, and for the second case, a zotarolimus eluting stent. Although SF appears to be more frequent after SES than other DES implantation, in lesions with high angulations, especially those in the right coronary artery, SF can occur in any type of stent. While no clinical trials have showed any advantage in changing the type of DES, this strategy has never been evaluated specifically in patients with SF.

In conclusion, this report illustrates two cases of EES restenosis secondary to stent fracture. Further studies should be performed to clarify whether this is an important issue or a sporadic observation.

References


Case Report

Stenting of Anomalous Left Main Coronary Artery Stenosis in an Adult with a Retroaortic Course

Lanjewar Charan, Santosh Shiradkar, P. G. Kerkar, and Agrawal Ashish

Department of Cardiology, King Edward VII Memorial Hospital, Acharya Donde Marg, Parel, Mumbai 400 012, India

Correspondence should be addressed to Lanjewar Charan, charanlanjewar@hotmail.com

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Coronary bypass graft has been the conventional treatment of choice in anomalous left main coronary artery stenosis. We are reporting an interesting case with anomalous left main coronary artery originating from right aortic sinus having retroaortic course complicated by significant atherosclerotic narrowing of the vessel and its percutaneous management.

1. Case Report

A 58-year-old diabetic male presented with rest angina followed by syncope. Baseline ECG showed right bundle branch with no significant ST-T changes. However, cardiac troponin was elevated suggesting acute coronary syndrome. Transthoracic Echocardiography was unremarkable with no regional wall motion abnormalities at rest.

Cardiac catheterization with coronary angiography demonstrated anomalous origin of single coronary artery from right sinus of valsalva and dividing into left main and right coronary artery. After getting origin, LMCA had long retroaortic course with significant discrete stenosis in the mid-stem of it, dividing finally into left anterior descending artery and left circumflex artery. Etiology of coronary occlusion was atherosclerotic plaque and hence was present throughout cardiac cycle and no dynamic cause could be seen. Computerized tomography coronary angiography confirmed the anomalous left main artery origin and its course (Figure 1).

During intervention anomalous coronary was cannulated with 6F JR guiding catheter (Brite Tip Cordis company) and lesion was crossed with 0.014 angioplasty guide wire (Boston Scientific) and distally parked in the left circumflex artery. To provide the better support, another 0.014 BMW (Balance Middle Weight, Guidant Corporation) guide wire was kept in left anterior descending artery. Direct stenting was performed successfully with 3.5 × 12 mm drug eluting stent (Zotarolimus, Endeavour) at 14 atm (Figure 2). The procedure was uneventful and TIMI 3 flow achieved. The patient is doing very well and is asymptomatic at the recent clinical followup.

2. Discussion

Anomalies of the coronary arteries may be found incidentally in 0.3–1% of healthy individuals. Although coronary artery anomalies are far less common than acquired coronary artery disease, their impact on premature cardiac morbidity and mortality among adults is not trivial. In a study by Eckart et al. of 126 nontraumatic sudden deaths in young adults, cardiac abnormality was found in 64 cases (51%), with coronary artery abnormalities being the most common cardiac abnormality (39 of 64 patients (61%)) [1].

Our patient had hemodynamically significant anomalous left main coronary artery characterized by abnormalities of myocardial perfusion.

In the anomalous situation of a single coronary artery, only one coronary artery arises with a single ostium from the aortic trunk. This is an extremely rare congenital anomaly that is seen in only 0.0024% to 0.044% of the population. A single coronary artery may follow the pattern of a normal RCA or LCA, divide into two branches with distributions of the RCA and LCA, or have a distribution different from that of the normal coronary arterial tree [2].
Although a single coronary artery may be compatible with a normal life expectancy, patients are at increased risk for sudden death if a major coronary branch crosses between the pulmonary artery and the aorta. The four recognized patterns of an anomalous origin of a coronary artery from the opposite or noncoronary sinus are (a) the RCA arising from the left coronary sinus, (b) the LCA arising from the right coronary sinus, (c) the LCx or LAD artery arising from the right coronary sinus, and (d) the LCA or RCA (or a branch of either artery) arising from the noncoronary sinus, the involved artery may have a high or low takeoff.

In these anomalies, the coronary ostium may be at the normal level, or, moreover, a coronary artery arising from the opposite or noncoronary sinus can take any of the four common courses, depending on the anatomic relationship of the anomalous vessel to the aorta and the pulmonary trunk: (a) interarterial (i.e., between the aorta and the pulmonary artery), (b) retroaortic, (c) prepulmonic, or (d) septal (subpulmonic). It is of great clinical importance which course is taken. Although retroaortic, prepulmonic, and septal (subpulmonic) courses seem to be benign, an interarterial course carries a high risk for sudden cardiac death [3].

Our patient was having retroaortic course, where LMCA was coursing in the dorsal wall of the aorta and, subsequently, between aorta and left atrium.

The LMCA arises from the right sinus of Valsalva as a separate vessel or as a branch of a single coronary artery in 0.09% to 0.11% of angiographic studies, and in up to 75% of patients with this anomaly the course is interarterial putting them at high risk for sudden cardiac death due to the acute angle of the ostium, the stretch of the intramural segment, and the compression between the commissure of the right and left coronary cusps. However, this anomalous LMCA may also take a retroaortic, prepulmonic, or septal (subpulmonic) course [4].

The Bland-White-Garland syndrome (anomalous origin of the left coronary artery) arising from the pulmonary artery (ALCAPA syndrome) is a rare congenital condition. Eighty percent of affected infants die within 4 months. Survival is critically dependent on the development of collateral circulation. In adulthood, this syndrome is seen with angina, congestive heart failure, mitral regurgitation, and sudden death [5].

We decided to proceed with percutaneous management with stent because of very favorable anatomy of the lesion for PCI and stent placement, minimal operational trauma, and the expected good prognosis. The patient will be closely
followed up for determination of the benefit from stenting of left main coronary artery.

Guidelines mention that surgical correction is indicated in anamolous left coronary artery arising from right sinus of valsalva and having an interarterial course; however, there are no specific guidelines regarding which subset of patients should be treated percutaneously, but it is reasonable that young patients (<35 yrs old) presenting with acute coronary syndrome and diseased anomalous left main coronary artery should be managed with stenting. Coronary artery bypass graft is being increasingly viewed as less favourable option in light of the potential for competitive flow [6]. Patients with incidental diagnosis of anomalous coronaries without symptoms or inducible ischemia should be followed up closely [7].

3. Conclusion

Thus, stenting of anomalous left main coronary artery is feasible and a reasonably safe option, and it should be particularly considered in acute coronary syndrome with anoma- lous LMCA having retroaortic course. However, these patients should be followed up closely for restenosis.

Conflict of Interests

The authors hereby declare that none of them have any conflict of interests to disclose. This pertains to relationships with pharmaceutical companies, biomedical device manufacturers, or other corporations whose products or services are related to the subject matter of the paper. Such relationships include, but are not limited to, employment by an industrial concern, ownership of stock, membership on a standing advisory council or committee, being on the board of directors, or being publicly associated with the company or its products.

References

Clinical Study

Multiple Coronary Artery Thrombosis in 5,10-Methylenetetrahydrofolate Reductase Gene Mutation

Alfonso Campanile, Fabiola B. Sozzi, and Gian Battista Danzi

Department of Cardiology, Fondazione IRCCS Cà Granda, Ospedale Maggiore Policlinico, Via F. Sforza, 35 20122 Milano, Italy

Correspondence should be addressed to Alfonso Campanile, alfonsocampanile@hotmail.it

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1. Introduction

Simultaneous thrombosis of multiple epicardial coronary arteries is an uncommon angiographic finding in ST-segment elevation myocardial infarction. It is related to several factors such as diffuse vessel spasm, state of hypercoagulability, and a decreased coronary blood pressure [1].

Hyperhomocysteinemia is a risk factor of coronary artery disease associated to arterial thrombosis. It is characterized by an abnormally high concentration of homocysteine (a sulfurated amino acid produced through the methionine metabolism).

This paper describes a case of ST-segment elevation myocardial infarction secondary to thrombosis of two coronary arteries in a patient affected by intermediate hyperhomocysteinemia gene mutation related.

2. Case Presentation

A 42-year-old male presented at the emergency room of the Hospital Policlinico, Milan, Italy with chest pain. He did not have any medical disease including hypertension, diabetes mellitus, dyslipidemia, and denied cocaine abuse. He was a smoker with familial premature coronary artery disease history; his body mass index was 22.6. The vital signs were normal (blood pressure: 130/80 mmHg, heart rate: 73 bpm, and oxygen saturation: 100%), and physical examination revealed no abnormalities. A 2 mm ST-segment elevation in the inferior leads was documented at the electrocardiogram. After an initial medical treatment with unfractionated heparin, acetyl salicylic acid, and clopidogrel, the patient was transported to the catheterization laboratory. The coronary angiogram revealed a normal left main and circumflex artery and two luminal irregularities of right coronary artery (RCA) and left anterior descending artery (LAD) complicated by wide coronary thrombosis (Figures 1(a) and 1(c)). Then, a glycoprotein IIb/IIIa inhibitor was administered according to standard protocol and thrombus aspiration, followed by direct stent implantation in the mid-RCA and mid-LAD (resp., with two and one bare metal stent), which were successfully performed (Figures 1(b) and 1(d)). A transthoracic echocardiogram showed a mildly reduced left ventricular function (ejection fraction 53%) with a normal right ventricular size and function.

A moderately high plasma homocysteine level (>50 μmol/L) with normal serum vitamin B12 and folate levels were found at the biochemical analysis, together with normal renal and serum lipid profiles. A mild increase of
troponin T (peak 0.31 ng/mL, normal range: 0.00–0.03) was detected. The thrombophilia screening findings are shown in Table 1. The genetic testing for the methylenetetrahydrofolate reductase showed the presence of C677T mutation in homozygosis. Therefore, oral folic acid supplementation (5 mg/die) was initiated. Currently, a nine-month followup negative for cardiac events is recorded; the plasma homocysteine level remained at the upper normal limit after methionine treatment.

3. Discussion and Conclusion

Simultaneous multivessel thrombosis in the setting of acute myocardial infarction is a rare entity. A case of acute thrombosis of two simultaneous coronary arteries in a young adult with familial hyperhomocysteinemia is described.

Numerous studies have indicated that an increased plasma homocysteine level is a risk factor for occlusive arterial or venous disease [2–4].

Hyperhomocysteinemia usually occurs in people with at least one defective gene that affects the breakdown of homocysteine. There are two common defective genes in the population. The first one is related to the enzyme methylene-tetrahydrofolate reductase, the second to the methioninesynthetase. Other causes of hyperhomocysteinemia are represented by deficiency of vitamin B, impaired renal function, and negative lifestyle factors (smoking habit, coffee abuse, and sedentary lifestyle). [5, 6] Hyperhomocysteinemia is

<table>
<thead>
<tr>
<th>Tests</th>
<th>Results (normal range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prothrombin time</td>
<td>10.80 seconds (8.9–11.7)</td>
</tr>
<tr>
<td>International normalized ratio (INR)</td>
<td>0.96 (0.90–1.14)</td>
</tr>
<tr>
<td>Activated partial thromboplastin time</td>
<td>25.7 (24.5–35.2)</td>
</tr>
<tr>
<td>Homocysteine (Hcy)</td>
<td>&gt;50 μmol/L (4.00–15.40)</td>
</tr>
<tr>
<td>Protein C activity (%)</td>
<td>122% (72–160)</td>
</tr>
<tr>
<td>Protein S activity (%)</td>
<td>152% (79–183)</td>
</tr>
<tr>
<td>Antithrombin III activity</td>
<td>108.0% (82.0–112.0)</td>
</tr>
<tr>
<td>Factor V Leiden mutation</td>
<td>Negative</td>
</tr>
<tr>
<td>Prothrombin gene mutation</td>
<td>Negative</td>
</tr>
<tr>
<td>Phospholipid (cardiolipin) AB IgG</td>
<td>1.8 U/mL GPL (0–10)</td>
</tr>
<tr>
<td>Phospholipid (cardiolipin) AB IgM</td>
<td>0.0 U/mL MPL (0–10)</td>
</tr>
<tr>
<td>Lupus anticoagulant</td>
<td>Absent</td>
</tr>
</tbody>
</table>
classified as mild-moderate (15–30 μmol per liter), intermediate (>31–100 μmol per liter), and severe (>100 μmol per liter) [7].

Subjects with moderate hyperhomocysteinaemia are characterized by a prothrombotic, and dysfibrinolytic state and homocysteine level is an independent predictor of thrombotic events. [8] The oxidative injury of endothelium in homocysteinaemia, combined with the lack of vasculo-protective effects of nitric oxide, predisposes to thrombotic events [8]. It is now widely accepted that increased plasma homocysteine is associated with increased cardiovascular risk independently of other atherosclerosis risk factors. [9] However, it is still unclear whether plasma homocysteine can be approached as a modifiable risk factor for atherosclerosis [10]. Our patient showed elevated homocysteine levels associated with homozygosity for the C677T gene mutation of methylenetetrahydrofolate reductase. A significantly higher frequency of this genetic condition was found in patients with early coronary artery disease onset (age <45 years) [11]. Politi et al. presented a case of a 35-year-old patient, with extensive anterior AMI and multiple thrombotic occlusion (in the distal LAD, diagonal branches, and obtuse marginal branch). Also this case was associated to elevated homocysteine (in the distal LAD, diagonal branches, and obtuse marginal branch). Elevation myocardial infarction with concomitant multiple coronary arteries thromboses in a young patient with hyper-homocysteinaemia is a risk factor for recurrent venous thrombosis. Relation to coagulation and fibrinolytic parameters, "Thrombosis Research," vol. 70, no. 2, pp. 123–129, 1993.

No routine screening for elevated homocysteine and treatment is currently recommended except in patients who have premature atherosclerosis [13]. Further investigation on hyperhomocysteinaemia and coronary heart disease is needed.

Conflict of Interests

The authors declare that they have no conflict of interests.

References