Nonculprit Plaques in Patients With Acute Coronary Syndromes Have More Vulnerable Features Compared With Those With Non–Acute Coronary Syndromes: A 3-Vessel Optical Coherence Tomography Study

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Background—Patients with acute coronary syndrome (ACS) have a higher incidence of recurrent ischemic events. The aim of this study was to compare the plaque characteristics of nonculprit lesions between ACS and non-ACS patients using optical coherence tomography (OCT) imaging.

Methods and Results—Patients who had 3-vessel OCT imaging were selected from the Massachusetts General Hospital (MGH) OCT Registry. MGH registry is a multicenter registry of patients undergoing OCT. The prevalence and characteristics of nonculprit plaques were compared between ACS and non-ACS patients. A total of 248 nonculprit plaques were found in 104 patients: 45 plaques in 17 ACS patients and 203 plaques in 87 non-ACS patients. Compared with plaques of non-ACS patients, plaques of ACS patients had a wider lipid arc (147.3±29.5° versus 116.2±33.7°, P<0.001), a longer lipid length (10.7±5.9 mm versus 7.0±3.7 mm, P=0.002), a larger lipid volume index [averaged lipid arc×lipid length] (1605.5±1013.1 versus 853.4±570.8, P<0.001), and a thinner fibrous cap (70.2±20.2 μm versus 103.3±46.8 μm, P<0.001). Moreover, thin-cap fibroatheroma (64.7% versus 14.9%, P<0.001), macrophage (82.4% versus 37.9%, P<0.001), and thrombus (29.4% versus 1.1%, P<0.001) were more frequent in ACS patients. Although the prevalence of microchannel did not differ between the groups, the closest distance from the lumen to microchannel was shorter in ACS subjects than in non-ACS (104.6±67.0 μm versus 198.3±133.0 μm, P=0.027).

Conclusions—Nonculprit lesions in patients with ACS have more vulnerable plaque characteristics compared with those with non-ACS. Neovascularization was more frequently located close to the lumen in patients with ACS. (Circ Cardiovasc Imaging. 2012;5:433-440.)

Key Words: atherosclerosis ■ coronary disease ■ imaging ■ plaque

Pathological studies have demonstrated that plaque rupture with subsequent occlusive thrombus formation is a primary cause of acute coronary syndrome (ACS).1-3 Plaque vulnerability has been widely accepted as an underlying mechanism for this local phenomenon. However, plaque instability is not merely a local vascular accident but reflects a pan-vascular process with the potential to destabilize atherosclerotic plaques in nonculprit areas.4 Some studies have reported that ruptured and/or vulnerable plaques exist at nonculprit lesions, as well as in culprit segments in ACS patients.5-7 Moreover, patients who presented with ACS and underwent percutaneous coronary intervention had a similar recurrent adverse cardiovascular event rate in culprit lesions and nonculprit lesions (12.9% versus 11.6% during a 3-year follow-up period).8

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Neovascularization has been recognized as an important process in the progression of atherosclerotic plaque and has also been recently identified as an important feature of plaque vulnerability. Optical coherence tomography (OCT) has been shown to be able to identify various components of atheromatous plaques, including neovascularization.

The purpose of this study was to investigate the plaque characteristics of nonculprit lesions in ACS patients and compare them with those in non-ACS subjects.

Methods

Study Population

A total of 108 patients who underwent 3-vessel OCT imaging were identified from the Massachusetts General Hospital (MGH) OCT Registry database. The MGH OCT registry is a multicenter registry of patients undergoing OCT, composed of 20 sites across 6 countries (see the Online Data Supplement Acknowledgments). Patients with cardiac shock, congestive heart failure, chronic total occlusion, a left main disease, and renal failure were not enrolled. Patients incapable of giving consent were not included. Four patients were excluded due to poor image quality; 104 patients (96.3%) were included in the final analysis. The ACS group included ST-elevation-myocardial infarction (STEMI), non-STEMI, and unstable angina (UA); the non-ACS group included stable angina pectoris (SAP). STEMI was defined as continuous chest pain that lasted ≥30 minutes, arrival at the hospital within 12 hours from the onset of chest pain, ST-segment elevation >0.1 mV in ≥2 contiguous leads, or new left bundle-branch block on the 12-lead ECG and elevated cardiac markers (creatinine kinase-MB or troponin T/I). Non-STEMI was defined as ischemic symptoms in the absence of ST-elevation on ECG with elevated cardiac markers. SAP was defined as chest pain on exertion, positive stress test result, and no change in the frequency, duration, or intensity of symptoms within 4 weeks before admission. UA was defined as angina at rest, accelerated angina, or new-onset angina. Nonculprit lesions were defined as plaques viewed on an angiogram that had not been treated. Plaques with more than 30% diameter stenosis as compared with reference diameter by OCT were included in our study. Each plaque was separated by at least 5 mm from the edge of any other plaque or implanted stent edge. The registry was approved by each institutional review board committee and all patients provided informed consent before enrollment.

Acquisition of OCT Images

Images were acquired using a commercially available time-domain (M2/M3 Cardiology Imaging System, LightLab Imaging, Inc, Westford, MA) or frequency-domain (C7-XR OCT Intravascular Imaging System, St Jude Medical, St Paul, MN) OCT system. The intracoronary OCT imaging technique has been described previously. In brief, the M2/M3 system uses an occlusion balloon (Helios, LightLab Imaging, Inc) that is inflated proximal to the lesion at 0.4 to 0.6 atm during image acquisition. The imaging wire is automatically pulled back from a distal to a proximal position at a rate of 1.0 to 3.0 mm/s, and saline is continuously infused from the tip of the occlusion balloon. In the C7 system, a 2.7F OCT imaging catheter (Dragonfly, LightLab Imaging, Inc) is advanced distal to the lesion, and automatic pull-back is initiated in concordance with blood clearance by the injection of contrast media or Dextran. All images were deidentified and digitally stored.

OCT Data Analysis

Plaques were classified into 2 categories: (1) fibrous (homogeneous high signal region) or (2) lipid plaque (low signal region with diffuse border). When lipid was present ≥90° in any of the cross-sectional images within the plaque, it was considered a lipid-rich plaque (Figure 1A). In lipid-rich plaque, lipid arc was measured at every 1-mm interval throughout the entire length of each lesion and the values were averaged. Lipid length was also measured on longitudinal view. Lipid volume index was defined as the averaged lipid arc multiplied by lipid length. The fibrous cap thickness (FCT) of lipid-rich plaque was measured at its thinnest part 3 times, and the average value was then calculated. Thin-cap fibroatheroma (TCFA) was defined as the thinnest fibrous cap thickness ≤65 μm in lipid-rich plaque on a cross-sectional image (Figure 1A). Macrophage infiltration was defined as bright spots with high OCT backscattering signal variances (Figure 1B). A microchannel was defined as a black hole or a tubular structure within a plaque (Figure 1C). Microchannels were measured using the shortest distance between the lumen and microchannel on each cross-sectional image, and the closest distance in the patient was compared between the groups. The presence was also recorded (Figure 2). Plaque disruption was identified by the presence of fibrous cap discontinuity with a clear cavity formed inside the plaque. Intracoronary thrombus was defined as a mass (diameter ≥250 μm) attached to luminal surface or floating within the lumen, including red (red blood cell-rich) thrombus (Figure 1D), which was highly backscattering with high attenuation (resembles blood), and white (platelet-rich) thrombus, which was less backscattering and homogeneous with low attenuation (Figure 1E). Calcification was recorded when an area with low backscatter signal and a sharp border was identified inside a plaque (Figure 1F). Macrophage, plaque disruption, thrombus, and calcification were recorded only for their presence. The OCT data were analyzed at an independent MGH OCT core laboratory by 2 experienced investigators who were blinded to the angiographic and clinical findings using proprietary software (LightLab Imaging, Inc). When there was discordance between the investigators, a consensus reading was obtained from a third independent investigator. Intracoronal correlation coefficient for interobserver and intraobserver reliabilities of lipid arc were 0.844 and 0.903, respectively.

Statistical Analysis

All statistical analysis was performed by an independent statistician at a core laboratory. For the analysis of patient characteristics, categorical data are presented as frequencies (percentages) and were compared using a χ² test or Fisher exact test, depending on the data. Continuous measurements are presented as means±SD and median (25th to 75th percentiles). Means of the continuous measurements were compared using the Student t test. To compare plaque characteristics between ACS and non-ACS patients, Generalized Estimating Equations approach were used to take into account the intraclass correlation due to the multiple plaques analyzed within a single patient’s data. Analysis of receiver operating characteristics (ROC) was used to determine the predictability (sensitivity and specificity) of the distance from the lumen to microchannel. Intraobserver and interobserver reliabilities were estimated by intraclass correlation coefficient for continuous measurement. All analysis was performed using SAS 9.1.3, with a probability value <0.05 considered statistically significant.

Results

Baseline Characteristics

Baseline patient characteristics are shown in the Table. The ACS group consisted of 17 patients (7 STEMI and 10 UA/non-STEMI); the non-ACS group consisted of 87 SAP patients. A higher frequency of current smoking and less frequent usage of statin were observed in the ACS group as compared with the non-ACS group. The level of low-density lipoprotein cholesterol (LDL-C) was higher and that of high-density lipoprotein cholesterol (HDL-C) was lower in the ACS group. Despite 3-vessel imaging, no procedure related complications were reported from any institution.
A total of 248 nonculprit plaques were found in 104 patients: 45 plaques in 17 ACS patients (2.7±1.3 plaques/patient) and 203 plaques in 87 non-ACS patients (2.3±1.1 plaques/patient). Although the number of plaques per patient did not differ between the groups, the number of lipid-rich plaques per patient was greater in the ACS group than in the non-ACS group (1.9±1.4 versus 1.1±1.1, \(P=0.013\)) (Table). The distribution of plaques among the 3 coronary arteries was not different between the 2 groups: 42.3% of plaques were located in the right coronary artery, 34.3% of plaques in the left anterior descending artery, and 23.4% of plaques in the left circumflex artery.

**OCT Findings**

A total of 248 nonculprit plaques were found in 104 patients: 45 plaques in 17 ACS patients (2.7±1.3 plaques/patient) and 203 plaques in 87 non-ACS patients (2.3±1.1 plaques/patient). Although the number of plaques per patient did not differ between the groups, the number of lipid-rich plaques per patient was greater in the ACS group than in the non-ACS group (1.9±1.4 versus 1.1±1.1, \(P=0.013\)) (Table). The distribution of plaques among the 3 coronary arteries was not different between the 2 groups: 42.3% of plaques were located in the right coronary artery, 34.3% of plaques in the left anterior descending artery, and 23.4% of plaques in the left circumflex artery.

Plaque-based comparison of OCT findings between ACS and non-ACS groups is shown in Figure 3. Compared with plaques of non-ACS patients, those of ACS patients had a wider lipid arc (147.3±29.5°, [148.2 (124.3–171.0)] versus 116.2±33.7°, [107.7 (93.7–135.9)], \(P<0.001\)), a longer lipid length (10.7±5.9 mm, [8.1 (6.5–14.2)] versus 7.0±3.7 mm, [6.0 (4.1–9.1)], \(P=0.002\)), a larger lipid volume index (1605.5±1013.1, [1335.3 (815.3–2147.1)] versus 853.4±570.8, [684.1 (402.3–1215.8)], \(P<0.001\)), and thinner fibrous cap (70.2±20.2 μm, [63 (60.0–70.0)] versus 103.3±46.8 μm, [90 (70.0–120.0)], \(P<0.001\)). In addition, lipid-rich plaque (71.1% versus 47.3%, \(P=0.005\)) and TCFA (44.4% versus 6.9%, \(P<0.001\)) were more frequent in ACS plaques.

Patient-based analysis of OCT plaque characteristics in ACS and non-ACS are summarized in Figure 4. TCFA (64.7% versus 14.9%, \(P<0.001\)), macrophage (82.4% versus 37.9%, \(P<0.001\)), and thrombus (29.4% versus 1.1%, \(P<0.001\)), were more frequent in ACS patients. Although the prevalence of disruption of nonculprit lesions was not statistically different between the groups, the incidence was more than doubled in ACS patients compared with non-ACS patients (35.3% versus 12.6%, \(P=0.051\)). No difference in the incidence of calcification was observed. Although the prevalence of microchannels did not differ between the groups (64.7% versus 55.2%, \(P=0.647\)), the closest distance from the lumen to microchannel in the patient was significantly shorter in ACS subjects (104.6±67.0 μm, [80 (62.5–117.5)] versus 198.3±133.0 μm, [165.0 (95.0–240.0)], \(P=0.027\)). ROC analysis demonstrated that the distance of 130 μm separates ACS patients with a sensitivity and specificity of 87.5% and 68.0%, respectively (area under the curve: 0.808, \(P<0.001\); 95% confidence interval, 0.693–0.895).
Discussion

The present study detailed plaque characteristics in non-culprit lesions in patients with ACS using 3-vessel OCT imaging and compared the findings with those of non-ACS subjects to understand the underlying pathophysiology of higher recurrent ischemic events in the ACS population. It is known that ACS patients are at high risk for recurrent ischemic events caused by a lesion that is anatomically unrelated to the initial event.\(^4\) Inflammation may play a central role in these patients;\(^22,23\) however, previous studies lack a detailed description of plaque morphology to explain the higher recurrent ischemic events. Our analysis demonstrated that nonculprit lesions in the ACS subjects, as compared with non-ACS, have a larger lipid volume, a thinner fibrous cap, and higher prevalence of TCFA. Thrombus and macrophage were also more frequent in the ACS group. Although the number of plaques per patient did not differ between the 2 groups, the number of lipid-rich plaques per patient was greater in ACS patients. All of these findings coincide with the typical pathological features of plaque vulnerability.\(^3\) Therefore, our study supports the concept that ACS is a pan-vascular process with a higher prevalence of vulnerable plaques in nonculprit sites, leading to recurrent ischemic events in the future.\(^4\) To our knowledge, our study is the first report that describes detailed plaque characteristics of nonculprit lesions in all 3 coronary arteries. Our results provide rationale that more aggressive plaque stabilization therapy such as cholesterol lowering and/or anti-inflammatory agents may be of additional value in ACS patients.

The Prevalence of Lipid-Rich Plaques

In the present study, not only the number of lipid-rich plaques per patient was greater (1.9±1.4 versus 1.1±1.1, \(P=0.013\)), but also the prevalence of lipid-rich plaque was higher (71.1% versus 47.3%, \(P=0.005\)) in the ACS group. A large lipid pool with a thin fibrous cap and heavy infiltration of macrophages are the major components of a vulnerable plaque.\(^3\) Angioscopic studies have reported that 89% to 95% of plaques in ACS were yellow plaques compared with 57% to 64% of plaques in SAP.\(^5,24\) In vivo OCT study has been reported that the prevalence of lipid-rich plaque was 90% in STEMI, 75% in NSTEMI/UA, and 59% in SAP.\(^14\) Our study demonstrates that 3 of 4 nonculprit plaques of ACS contain large amount of lipid.

Lipid Volume

Positive remodeling, large plaque burden, and larger lipid core are well-described characteristics of vulnerability.\(^3,25\) Integated backscatter intravascular ultrasound (IB-IVUS) studies reported that both culprit and nonculprit lesions of ACS patients had a higher percent lipid (lipid area/plaque area) and a lower percent fibrous (fibrous area/plaque area) compared with non-ACS patients.\(^26\) In the present study, nonculprit plaques of ACS had a wider lipid arc, a longer lipid length, and a larger lipid volume index. Our findings that plaques with ACS have larger lipid volume compared with non-ACS are consistent with the previous studies.

TCFA and Macrophage

In the present study, the prevalence of TCFA was higher in ACS patients than in non-ACS patients (64.7% versus 14.9%,
respectively, \( P < 0.001 \)). Our group reported the first in vivo comparison of culprit plaque characteristics between ACS and non-ACS patients using OCT. TCFA was more frequent in STEMI (72\%) and non-STEMI/UA (50\%) than in SAP (20\%) in their culprit lesions. Hong et al\(^{27}\) reported, using virtual histology intravascular ultrasound (VH-IVUS), that 72\% of ACS patients and 54\% of SAP patients had VH-TCFA. The PROSPECT study using 3-vessel gray-scale IVUS and VH-IVUS in ACS patients demonstrated that 46.7\% ACS patients had VH-TCFA in their nonculprit lesions, moreover the presence of TCFA was a strong independent predictor of recurrent cardiac events.\(^{28}\) Kubo et al\(^{29}\) reported that the prevalence of TCFA by OCT in nonculprit lesions was 38.5\% in ACS patients and 6.3\% in non-ACS patients. The prevalence of TCFA in non-culprit lesions was higher in our study compared with Kubo’s reports. The most likely explanation for this discrepancy is that we examined all 3 vessels in our study, whereas Kubo performed OCT in only 1 or 2 vessels.

Our study also demonstrates that macrophage infiltration was more frequent in ACS patients than in non-ACS patients. Autopsy data of coronary plaques from sudden cardiac death identified that the macrophages have been implicated in every stage of coronary atherosclerosis from its initiation to its clinical presentation.\(^{23,29}\) Macrophages secrete matrix metalloproteinase, which may destabilize plaque,\(^{30}\) and expresses tissue factor, a potent promoter of coagulation.\(^{31}\) Increased macrophages within culprit lesions have been seen more frequently in autopsy studies of ACS patients compared with those of stable patients.\(^{3,32}\) Our group previously reported in a small number of patients that macrophage infiltration was greater in ACS nonculprit sites as compared with those of non-ACS patients.\(^{19}\) The present data extended the previous conclusions that inflammatory cell activation was not only in the culprit artery but was also found in the nonculprit vessels,\(^{3,32}\) indicating the multifocal nature of inflammation in ACS plaques.

**Microchannels**

Neovascularization has been recognized as an important process for the progression of atherosclerotic plaques and has also been identified recently as one of the features of plaque vulnerability.\(^{8,10}\) On OCT images, neovascularization was observed as a small black hole or a tubular structure within a plaque, similar to a microchannel. In the present study, the

**Figure 3.** Plaque-based comparison of optical coherence tomography findings between acute coronary syndrome (ACS) and non-ACS plaques. ACS patients had a wider lipid arc (\( P < 0.001 \)), a longer lipid length (\( P = 0.002 \)), and a larger lipid volume, and a thinner fibrous cap (\( P < 0.001 \)) compared with non-ACS patients. Lipid-rich plaque (71.1\% versus 47.3\%, \( P = 0.005 \)) and thin-cap fibroatheroma (TCFA) (44.4\% versus 6.9\%, \( P < 0.001 \)) were more frequent in ACS compared with non-ACS.

**Figure 4.** Patient-based analysis of plaque characteristics in acute coronary syndrome (ACS) and non-ACS. ACS patients had more frequent of thin-cap fibroatheroma (TCFA) (\( P < 0.001 \)), macrophage (\( P = 0.001 \)), and thrombus (\( P < 0.001 \)) compared with in the non-ACS patients. The prevalence disruption calcification and microchannels did not differ between the groups. The closest distance from microchannel to lumen was shorter in ACS patients than non-ACS (\( P = 0.027 \)).
overall prevalence of microchannels in nonculprit lesions was not significantly different between ACS and non-ACS patients (64.7% versus 55.2%, respectively, \( P=0.647 \)). However, the closest distance from the lumen to microchannel in the patient was shorter in ACS subjects than in non-ACS. ROC analysis demonstrated that the distance of 130 \( \mu \text{m} \) separates ACS from non-ACS patients with the sensitivity and specificity of 87.5% and 68.0%, respectively.

Intimal neovascularization is a common feature of atherosclerotic disease, correlating with histological alterations and symptoms. Neovascularization density increased in lesions with marked macrophage infiltration of TCFA, lipid-rich lesions, and lesions with intraplaque hemorrhage and rupture. All features are related to plaque vulnerability. Neovascularization facilitates blood-derived inflammatory cells to reach atherosclerotic plaques. Furthermore, inflammation also increases microangiogenic activity and amplifies macrophage recruitment. The majority of neovascularization derives from the adventitial vasa vasorum in the early stage of atherosclerosis and penetrates into the intima as the plaque progresses. Considering the location of microchannels, which was closer to the lumen in ACS patients, it is reasonable to speculate that plaque instability might be related to the location of neovascularization within the plaques. Therefore, the plaque with neovascularization located closer to the lumen might represent an advanced stage of atherosclerosis. Recently, it was reported that OCT can detect neovascularization; however, rigorous systematic validation studies using histology as the gold standard would be warranted.

**Disruption**

Although the prevalence of disruption of nonculprit lesions was not statistically different between ACS and non-ACS groups, the incidence was more than double in ACS patients compared with non-ACS (35.3% versus 12.6%). Several IVUS studies have reported that plaque rupture was observed not only in the culprit lesion but also in nonculprit sites. Rioufol et al showed that 79% of ACS patients had ruptured plaque in nonculprit lesions. Hong et al reported, in a 3-vessel IVUS study, that 17% of ACS patients had ruptured plaques in nonculprit lesions, compared with 5% of non-ACS patients. Tanaka et al reported that multiple plaque disruption was associated with systemic inflammation and that patients with multiple plaque rupture had poor prognosis. Although plaque disruption is thought to be the main contributing factor of plaque instability, the exact incidence of plaque disruption is still unknown. To the best of our knowledge, our study is the first to demonstrate the prevalence of plaque disruption in nonculprit lesions by 3-vessel OCT imaging.

Epidemiological studies have demonstrated that high levels of LDL-C and low levels of HDL-C predict cardiovascular risk and have confirmed the benefit of cholesterol-lowering therapy with statins in high-risk patient populations. In the present study, although the incidence of hyperlipidemia was not significantly different, ACS patients had a higher level of LDL-C and lower level of HDL-C; moreover, the usage of statin therapy was less frequent. These lipid profiles and a less frequent use of statin might have also affected pan-vascular process with a higher prevalence of vulnerable plaques in nonculprit sites of ACS subjects. More aggressive lipid-lowering therapy with statin may have an additional value in this population.

**Limitations**

First, this was a retrospective study, using a registry database. Therefore, there was obvious selection bias. Second, due to the relatively shallow axial penetration, exact measurements of necrotic core and plaque burden by OCT were not possible. However, since the most important morphological determinants of plaque vulnerability are superficial, the region of greatest interest was still within the imaging range of the current OCT system. Third, disruption, microchannels, macrophages, thrombus, and calcification were not quantified and not rigorously validated. Fourth, the sample size was small due to 3-vessel OCT imaging. Since it was practically difficult to perform 3-vessel OCT imaging using the first-generation OCT system in unstable patients, the number of ACS patients was small. Fifth, although OCT imaging was performed in 3 vessels, most segments imaged did not include the distal segment and occasionally very proximal segment. Sixth, ACS patients had a higher level of LDL-C and lower of HDL-C, moreover, the usage of statin therapy was less frequent in this patient population. Seventh, patients were randomly selected for image analysis; however, vessel analysis within the same patient was not performed in a random sequence. Finally, no power calculation was performed.

**Conclusions**

Nonculprit plaques in patients with ACS have more vulnerable plaque characteristics compared with those in non-ACS patients. This finding supports the concept that plaque vulnerability is a pan-vascular phenomenon in patients with ACS. The data provide direct support for current guidelines recommending aggressive management of lipids in patients with ACS.

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**Disclosures**

Dr Jang received a research grant and consulting fee from LightLab Imaging/St Jude Medical. Dr Zhang is an employee of LightLab Imaging/St Jude Medical.

**References**


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Patients with acute coronary syndrome (ACS) have a higher rate of recurrent ischemic events. Although it has been speculated that nonculprit plaques in ACS patients would have higher levels of plaque vulnerability, this concept has not been proven due to the lack of diagnostic modality. In the current study, an attempt was made to prove this hypothesis in vivo, using a high-resolution intravascular imaging modality: optical coherence tomography. Indeed, nonculprit lesions in the ACS subjects, as compared with non-ACS, have features consistent with plaque vulnerability: larger lipid volume, thinner fibrous cap, and a higher prevalence of thin-cap fibroatheroma, thrombus, macrophage, and superficial microvessels. This study supports the concept that ACS is a pan-vascular process with a higher prevalence of vulnerable plaques in nonculprit sites, which explains the higher recurrent ischemic events. Therefore, a more aggressive plaque stabilizing treatment such as cholesterol lowering and/or anti-inflammatory therapy may have additional value in ACS patients.
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In Search of Vulnerable Plaque

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Between 1970 and 2010, the number of cardiovascular deaths per 100,000 persons in the United States has fallen from ≈450 to ≈125, a reduction >70%. This marked decline in cardiovascular mortality represents one of the true success stories of modern medicine. The improving lifespan of both men and women can be attributed principally to prevention of death first from coronary artery disease (CAD) and second from stroke, with a much smaller contribution from other disease states. The decrease in coronary heart disease deaths may be ascribed to both treatment of acute coronary syndromes (ACS) and chronic CAD as well as risk-factor modification. Nonetheless, we remain in the midst of a coronary epidemic, with >2200 deaths per day in the United States because of cardiovascular disease (≈1 death every 39 seconds).

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Coronary plaque thrombosis is found in most patients dying of cardiovascular death. Those plaques which are at high risk for imminent thrombosis (whether the risk period is days, weeks, or months) are termed “vulnerable plaques.” Although atherosclerosis is a pan-vascular process arising from systemic inflammation, vulnerable plaques are not present diffusely but are limited in number and are most commonly located in the proximal and midsegments of the epicardial coronary vessels (and distal in the right coronary artery). Although several plaque types have been identified which are prone to thrombosis, pathological studies have found that the majority of such plaques are thin cap fibroatheromas (TCFAs), characterized by a large necrotic core with a thin (<65 µm) fibrous cap consisting of mostly type 1 collagen with few smooth muscle cells, infiltrated with macrophages and T lymphocytes. Cellular production of matrix metalloproteinases and other digestive enzymes, exacerbated by high shear and focal cap calcification, results in plaque rupture, leading to tissue factor release and superimposed thrombus formation. Conversely, pathological intimal thickening, fibrotic, and fibrocalcific plaques are less commonly found at the site of coronary thrombosis. A necrotic core-containing fibroatheroma with a thick fibrous cap is believed to be intermediate in risk. Over the past 2 decades, this knowledge has prompted widespread efforts to identify in vivo the structural/morphological, chemical, and physical properties of the TCFAs, with the goal of ultimately developing therapies to prevent acute myocardial infarction and sudden cardiac death.

Whereas numerous candidate noninvasive testing modalities have been proposed (the farthest along being multidetector computerized tomography), greater signal-to-noise ratio may be achieved by placing an intravascular imaging device adjacent to an atheroma. Numerous such catheters have been evaluated in humans, with most failing for a variety of device-specific, practical or commercial reasons, including thermography, intravascular magnetic resonance imaging, palpography, angioscopy, and vasa vasorum imaging. However, 3 such devices have emerged and have received Food and Drug Administration approval with “tool” claims that are theoretically capable of identifying certain characteristics of a TCFAs: radiofrequency intravascular ultrasound (RF-IVUS), optical coherence tomography (OCT), and near-infrared spectroscopy (NIRS). Unlike gray-scale IVUS, which analyzes only the amplitude of the back-scattered sound waveform, RF-IVUS incorporates frequency domain information, providing greater diagnostic accuracy. OCT is similar to IVUS but uses light as a probe rather than sound, affording substantially greater axial resolution (10–20 µm rather than 150–200 µm), although sacrificing depth of penetration. NIRS analyzes the underlying chemical signature of the atheroma and has been tuned to identify “lipid core plaque” or necrotic core. Unlike RF-IVUS and OCT, NIRS does not create a tomographic image of the lesion but rather displays a “chemogram” of the vessel wall according to a weighted composite spectroscopic signature from the intima to adventitia. All 3 devices create interesting cross-sectional, longitudinal, and sagittal images purporting to represent high-risk human coronary atheroma. So how should these imaging tools be validated as potential detectors of vulnerable plaque?

For decisive confidence that the image created by a noninvasive or invasive modality truly represents vulnerable plaque, a 4-step process is required. First, human autopsy coronary mapping studies should be performed to ensure that the device is able to identify specific tissue components of atherosclerotic plaque with reasonable accuracy, first on a pixel-by-pixel basis and then on a lesion level (plaque phenotype recognition). Second, most plaques responsible for ACS should be shown at the time of the event to have the imaging characteristics consistent with a pathological ruptured TCFAs (with thrombus), whereas most plaques responsible for stable CAD syndromes should lack these features. A complementary approach is to demonstrate that a higher proportion of non-culprit lesions (NCLs) in patients with ACS compared with stable CAD are fibroatheromas, which has been demonstrated pathologically. Third, prospective natural history studies must be performed in which NCLs are classified by imaging as either high risk (vulnerable) or not and followed longitudinally to determine whether such imaging representations do indeed identify lesions prone to future rapid lesion progression, rupture, thrombosis, and major adverse cardiac events (MACE). Finally, and most ambitiously, ≥1 systemic or focal/regional therapies for the alleged vulnerable plaques as identified by the...
imaging tool should be shown to prevent future MACE, as tested in prospective, randomized trials.

RF-IVUS, OCT, and NIRS have been demonstrated, in vitro, to be capable of identifying plaque components compared with histology, and are reasonably accurate for plaque phenotype characterization. Evidence has been presented that each modality identifies its version of vulnerable plaque as being present in the majority of patients with ACS. To date, only RF-IVUS has been demonstrated in prospective natural history studies to be capable of identifying lesions responsible for future MACE. No trials have been initiated to determine whether treating “at-risk” plaques improves long-term lesion-specific or patient outcomes.

In this issue of Circulation: Cardiovascular Imaging, Kato et al provide important new insights regarding the morphology of NCLs in patients with ACS versus stable CAD. From a prospective, multicenter registry in which 3-vessel OCT imaging was performed, with the images analyzed at a blinded core laboratory, the authors convincingly demonstrate that compared with NCLs in patients with stable CAD, NCLs in ACS patients have a wider lipid arc with longer lipid length and with thinner fibrous caps. NCL TCFAs were more frequently identified in patients with ACS than non-ACS, as were undiagnosed plaque ruptures with thrombus. These data thus complement reports from prior studies with RF-IVUS and NIRS. Furthermore, the present study provides novel insights, demonstrating that NCLs in ACS patients more frequently have macrophages present and microchannels adjacent to the lumen. Although the specificity of OCT for macrophage detection may be questioned and the implications of microchannel lumen proximity are unknown (especially as the presence of microchannels was not statistically different between the 2 groups), the company that these measures keep (extensive lipid with thin fibrous caps) adds credence to their potential involvement in the vulnerable plaque process.

Although the authors acknowledge important limitations of their study (including selection bias, relatively few ACS patients, nonquantitative evaluation of several key components and missing data from the most proximal segments of the coronary tree, where TCFAs are pathologically known to reside), other issues should be addressed. First, the major drawback of OCT is its limited penetration depth and inability to assess plaque volume. The authors minimize this limitation by stating that “the most important morphological determinants of plaque vulnerability are superficial.” This may not be true; in the study, Providing Regional Observations to Study Cardiac Events (PROSPECT), the most important independent determinant of future MACE was plaque burden; the same finding was subsequently reported by the VIRUS in Vulnerable Atherosclerosis (VIVA) investigators. Similarly, “lipid volume index” by OCT was defined as the averaged lipid arc multiplied by lipid length—this is at best a poor surrogate for a true volume measure and should be renamed. Second, an important imbalance not emphasized was the higher use of statins in the stable CAD group, which has been demonstrated to increase fibrous cap thickness and decrease atheroma and lipid volume. The present analysis would benefit with multivariable correction of these and other baseline imbalances.

These comments notwithstanding, the authors should be congratulated for a carefully performed study that moves the field forward. However, numerous questions remain to be answered. Which lesion-based OCT characteristics from the present study (if any) are most strongly predictive of future MACE originating from that lesion? Lipid arc or length? Fibrous cap thickness? Macrophage density or microchannel parameters? A prospective natural history study is required to sort this out. What is the temporal stability of OCT-assessed vulnerable plaque parameters? RF-IVUS plaque composition and phenotype have been reported to evolve over a period of months (either to a more stable or unstable morphology). Can the findings from an OCT core laboratory be translated into the catheterization laboratory? In this regard, lipid versus calcium versus signal drop-out may be mischaracterized by nonexpert (and some expert) readers. Lack of blood clearance can be misconstrued as thrombus. Automated or semiautomated edge detection and pattern recognition software would be of great use. Are OCT parameters as or more predictive of plaque vulnerability than either RF-IVUS or NIRS parameters? Concordance between these different imaging modalities in assessing plaque characteristics and phenotype is far from perfect. Multiple modalities may provide synergistic information—for example, combining plaque burden data from IVUS with either fibrous cap thickness from OCT or lipid core plaque content from NIRS.

Most importantly, randomized trials must ultimately be undertaken in patients with high-risk plaques (identified by the imaging tool) to evaluate the use of either new more potent systemic therapies (perhaps representing a future role for proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors, because most patients with coronary atherosclerosis are already prescribed high-dose statins) or focal/regional interventional therapies (eg current drug-eluting stents, emerging bioabsorbable vascular scaffolds, or photodynamic therapy) to demonstrate that treating vulnerable plaques before rupture is effective in preempting future ACS, myocardial infarction, and cardiac death. If such data are absent, 3-vessel invasive screening as performed in PROSPECT and the current study cannot be recommended outside the research setting, given the small but inherent risks of the procedure (coronary dissection and extra contrast and radiation exposure). These considerations notwithstanding, the potential for further reducing the global burden from cardiovascular disease justifies the tremendous efforts being expended in the search for vulnerable plaque.

Disclosures

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References


Supplemental Material

Acknowledgements

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Participating sites in this registry can be found at:

http://www.massgeneral.org/heartcenter/research/researchlab.aspx?id=1403