In Vivo Characterization of Coronary Atherosclerotic Plaque by Use of Optical Coherence Tomography

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Background—The current understanding of the pathophysiology of coronary artery disease is based largely on postmortem studies. Optical coherence tomography (OCT) is a high-resolution (~10 μm), catheter-based imaging modality capable of investigating detailed coronary plaque morphology in vivo.

Methods and Results—Patients undergoing cardiac catheterization were enrolled and categorized according to their clinical presentation: recent acute myocardial infarction (AMI), acute coronary syndromes (ACS) constituting non–ST-segment elevation AMI and unstable angina, or stable angina pectoris (SAP). OCT imaging was performed with a 3.2F catheter. Two observers independently analyzed the images using the previously validated criteria for plaque characterization. Of 69 patients enrolled, 57 patients (20 with AMI, 20 with ACS, and 17 with SAP) had analyzable images. In the AMI, ACS, and SAP groups, lipid-rich plaque (defined by lipid occupying ≥2 quadrants of the cross-sectional area) was observed in 90%, 75%, and 59%, respectively (P=0.09). The median value of the minimum thickness of the fibrous cap was 47.0, 53.8, and 102.6 μm, respectively (P=0.034). The frequency of thin-cap fibroatheroma (defined by lipid-rich plaque with cap thickness ≤65 μm) was 72% in the AMI group, 50% in the ACS group, and 20% in the SAP group (P=0.012). No procedure-related complications occurred.

Conclusions—OCT is a safe and effective modality for characterizing coronary atherosclerotic plaques in vivo. Thin-cap fibroatheroma was more frequently observed in patients with AMI or ACS than SAP. This is the first study to compare detailed in vivo plaque morphology in patients with different clinical presentations. (Circulation. 2005;111:1551-1555.)

Key Words: arteriosclerosis □ coronary disease □ imaging □ plaque

A utopsy studies suggest that acute coronary events most commonly arise from the disruption of thin-cap fibroatheromas (TCFA), known as vulnerable plaques. The pathological features of the most common form of vulnerable plaques include a large lipid pool inside a plaque, a thin fibrous cap, and increased macrophage infiltration within the cap, resulting in expression of proteolytic enzymes that weaken the fibrous cap and ultimately promote plaque disruption. Plaque disruption allows thrombogenic substrates, such as tissue factor and von Willebrand factor, to be exposed to the coronary circulation, resulting in the formation of a platelet-rich thrombus. When the thrombus becomes occlusive, in the absence of collateral blood supply, myocyte ischemia ensues, leading to an acute myocardial infarction (AMI) or acute coronary syndromes (ACS). Conversely, stable angina pectoris (SAP) is thought to arise from angiographically severe or flow-limiting stenoses without plaque disruption or local thrombus formation. As such, SAP is thought to represent a simple mismatch of blood supply and demand. Although widely accepted, these paradigms are based largely on postmortem studies, because it has previously not been possible to accurately define coronary plaque morphology in vivo on a microscopic scale.

Optical coherence tomography (OCT) is an optical analogue of intravascular ultrasound that allows high-resolution (~10 μm) tomographic intra-arterial imaging. The OCT characteristics for various components of atheromatous plaque have been validated in a histology-controlled study. Furthermore, we have demonstrated the feasibility of OCT imaging in patients undergoing percutaneous coronary intervention (PCI). The aim of the present study was to use OCT to evaluate the characteristics of culprit lesions in living patients with various clinical presentations.

Methods

Study Population

Patients with an identifiable culprit lesion in a native coronary artery were enrolled. Patients were excluded if they had significant left
main disease, congestive heart failure, or renal insufficiency with baseline serum creatinine \(>1.8\) mg/dL (\(>133\) \(\mu\)mol/L) or required emergency or primary angioplasty. In addition, those with extremely tortuous vessels or with heavy calcification were excluded because of expected difficulty in advancing the OCT catheter. Intravascular ultrasound was performed before OCT imaging. Therefore, when the intravascular ultrasound imaging was not successful because of anatomic reasons, no attempt was made to advance the OCT catheter. The patients were categorized on the basis of their clinical presentation: ST-elevation AMI within the preceding 2 weeks, ACS or a 1-way ANOVA, as appropriate. The frequency of various types of plaques or of TCFA was compared between groups by use of \(\chi^2\) test or Fisher exact test. To control for multiple comparisons, pairwise tests of frequency were performed only if the contingency table for all 3 types of disease was significant. Because cap thickness was not normally distributed, a Kruskal-Wallis test was performed to test for significant differences of cap thickness with respect to the clinical presentation. Intraobserver and interobserver variabilities were measured by \(\kappa\) test of concordance. All analysis was performed using Statistical Analysis Software version 8 (SAS Institute). A \(P<0.05\) was required for statistical significance.

Results

A total of 69 patients were enrolled in the study. Twelve patients were excluded because imaging was performed only after PCI (\(n=7\)), the image quality precluded analysis (\(n=4\)), or the equipment malfunctioned (\(n=1\)). Among the remaining 57 patients with successful OCT imaging before coronary intervention, 20 patients presented with recent AMI, 20 patients with ACS, and 17 patients with SAP.

Baseline Characteristics

No significant differences were found in the demographic or baseline characteristics, including coronary risk factors, between the groups (Table 1). The distributions of the culprit artery were comparable among the groups.

![Figure 1](https://circ.ahajournals.org/)

**Figure 1.** OCT images of 3 different types of atherosclerotic plaques. A, Lipid-rich plaque (L) covered by thin fibrous cap (arrow, magnified inset). B, Another type of lipid-rich plaque, but with thick fibrous cap. C, Dense, eccentric fibrous plaque (F) with no lipid component. A signal-rich, homogeneous reflective pattern is typical for fibrous tissue. In regions with no plaque (between 7 and 10 o’clock positions), intima, media, and adventitia are clearly visualized.

![Figure 2](https://circ.ahajournals.org/)

**Figure 2.** Examples of plaque disruption in patients with recent myocardial infarction. A, Large lipid-rich plaque (L) with localized rupture of a fibrous cap with a flap protruding into lumen (arrow). B, Severe disruption of plaque (arrows) with a large mural thrombus (T). Lipid is present in whole circumference (L). G indicates guidewire artifact.
In the AMI group, the average time interval between the onset of symptoms and OCT imaging was 4.6/5.3 days. All AMI patients were initially managed medically, without primary PCI. Thrombolysis was administered in 8 patients, and the combination of a thrombolytic agent and a glycoprotein IIb/IIIa inhibitor was administered in 2 additional patients. Six patients received a glycoprotein IIb/IIIa inhibitor without thrombolysis. The combination of aspirin and heparin was used in 2 patients who were clinically stable after a late presentation. Eight patients had postinfarction recurrent angina. In the ACS group, the average time delay between the symptom onset and imaging was 3.3/1.7 days, excluding 1 patient who was imaged 3 weeks after the acute episode.

### OCT Imaging

The OCT findings are summarized in Table 2. There was a trend toward higher frequency of lipid-rich plaque in patients with AMI or ACS compared with those with SAP. There were, however, significant differences among the groups with respect to the median values (range) for the minimum fibrous cap thickness: 47.0 (25.3 to 215.5) μm in the AMI group, 53.8 (18.7 to 184.3) μm in the ACS group, and 102.6 (22.0 to 291.1) μm in the SAP group, \( P = 0.034 \). In addition, cap thicknesses were significantly different between the AMI and SAP groups \( (P = 0.019) \) and the ACS and SAP groups \( (P = 0.043) \) but not between the AMI and ACS groups \( (P = 0.38) \). The frequency of TCFA was also significantly different among the groups (72%, 50%, and 20%, in the AMI, ACS, and SAP groups, respectively; \( P = 0.012 \) (Figure 3). TCFA frequency was significantly different between the AMI and SAP groups \( (P = 0.003) \) but not between the ACS and SAP groups \( (P = 0.049) \) or the AMI and ACS groups \( (P = 0.172) \). The percentage of patients with plaque disruption was not significantly different among the groups (25%, 15%, and 12%, in the AMI, ACS, and SAP groups, respectively). The difference in the frequency of calcification was significant among the groups (10% in the AMI group, 15% in the ACS group, and 41% in the SAP group, \( P = 0.049 \)). A thrombus was noted in 20% of the patients with AMI, 25% of those with ACS, and 35% of those with SAP.

### Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic, n (%)</th>
<th>AMI (n=20)</th>
<th>ACS (n=20)</th>
<th>Stable Angina (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y*</td>
<td>59.3±9.23</td>
<td>57.1±7.78</td>
<td>60.4±11.1</td>
</tr>
<tr>
<td>Male sex</td>
<td>16 (80)</td>
<td>16 (80)</td>
<td>16 (94)</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>10 (50)</td>
<td>11 (55)</td>
<td>8 (47)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5 (25)</td>
<td>3 (15)</td>
<td>5 (29)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10 (50)</td>
<td>10 (50)</td>
<td>11 (65)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>14 (70)</td>
<td>16 (80)</td>
<td>11 (65)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>29.1±4.3</td>
<td>32.0±6.4</td>
<td>29.8±5.1</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>13 (68)</td>
<td>6 (30)</td>
<td>10 (59)</td>
</tr>
</tbody>
</table>

Values are given as n (%) or *mean±SD. CAD indicates coronary artery disease; LAD, left anterior descending coronary artery; LCx, left circumflex artery; and RCA, right coronary artery.

### Table 2. OCT Findings

<table>
<thead>
<tr>
<th>Finding</th>
<th>AMI (n=20)</th>
<th>ACS (n=20)</th>
<th>Stable Angina (n=17)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid plaque, No. of quadrants</td>
<td>18</td>
<td>18</td>
<td>15</td>
<td>0.090</td>
</tr>
<tr>
<td>Lipid-rich plaque (≥2 quadrants)</td>
<td>18</td>
<td>15</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Fibrous cap thickness, μm*</td>
<td>47.0 (n=18)</td>
<td>53.8 (n=18)</td>
<td>102.6 (n=15)</td>
<td>0.034</td>
</tr>
<tr>
<td>TCFA</td>
<td>13 (n=18)</td>
<td>9 (n=18)</td>
<td>3 (n=15)</td>
<td>0.012</td>
</tr>
<tr>
<td>Plaque disruption</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>0.053</td>
</tr>
<tr>
<td>Calcification</td>
<td>2</td>
<td>3</td>
<td>7</td>
<td>0.049</td>
</tr>
<tr>
<td>Thrombus</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

TCFA indicates thin-cap fibroatheroma (lipid ≥2 quadrants+fibrous cap thickness ≤65 μm).

*Median.
All imaging procedures were performed without complication or adverse events. The average OCT imaging time per lesion site was less than 5 minutes.

**Intraobserver and Interobserver Variability**

Intraobserver variability yielded acceptable concordance for lipid-rich plaque (κ=0.86), plaque disruption (κ=0.68), calcification (κ=0.88), and thrombus (κ=0.74). Interobserver variability showed slightly lower concordance: lipid-rich plaque (κ=0.47), plaque disruption (κ=0.66), calcification (κ=0.57), and thrombus (κ=0.62).

**Discussion**

This is the first in vivo study of detailed coronary plaque morphology in patients with various clinical coronary presentations. This study also confirms the feasibility and safety of intravascular OCT for in vivo investigation of coronary atherosclerosis.

The findings of this study support our current understanding of the pathophysiology of coronary artery disease. Although there was a trend toward a higher frequency of lipid-rich plaque in patients with AMI or ACS compared with those with SAP, the differences were not statistically significant. Conversely, a significant difference was found in the thinnest fibrous cap thicknesses among the groups. The frequency of a TCFA was also significantly different among the groups. These findings indicate that although lipid is one of the main components for vulnerable plaque, thin fibrous cap may be a prerequisite for rupture of a plaque leading to AMI or ACS. This is consistent with previous pathological studies.

The frequency of plaque disruption was not significantly different between groups. This finding should be interpreted with caution, because we may have missed rupture locations because of the discrete sampling method used in this study and the possibility that the disruptions detected were iatrogenic. A recent intravascular ultrasound study demonstrated that 66% of patients with AMI had evidence of plaque rupture. This indicates that OCT probably underestimates the incidence of plaque rupture because of the discrete sampling method. The frequency of an intraluminal thrombus was not significantly different among the groups. This unexpected finding may have resulted from 2 factors. There was a time delay of up to 2 weeks between the acute event and imaging. It is possible that the prevalence of thrombus might have been higher had we imaged the plaques shortly after acute events in AMI or ACS patients. All the patients received thrombolytic or potent antithrombotic therapy. The combination of pharmacological intervention and an activated endogenous thrombolytic system could have dissolved some thrombi, especially in the AMI patients in whom the average delay between the acute event and the imaging was 4.6±5.3 days. In addition, with our thrombus size threshold of 250 μm, we could have detected small thrombi caused by a guidewire and therefore would have overestimated the frequency of thrombus in the stable angina patients. However, the finding of plaque rupture and thrombus in patients with stable angina is, in fact, not surprising. Similar findings were observed in previous angioscopic studies. This may help to explain the benefit of antiplatelet therapy in the stable angina patient population.

There are several potential applications of this new imaging modality. With its high resolution and unique characteristics, it is a powerful modality for detection of vulnerable coronary plaque. The most frequent variant of a vulnerable plaque is characterized by a lipid pool, a thin fibrous cap, and increased macrophage infiltration. Each of which can be detected by OCT. Quantitative analysis of these parameters over time may allow the monitoring of the effects of therapeutic interventions, including pharmacological therapy, gene therapy, or local mechanical therapy.

Another potential application of OCT is as an adjunct to PCI. Detailed structural information before and after coronary intervention can be evaluated with greater accuracy compared with intravascular ultrasound. Over the past decade, the number of interventional devices and techniques has increased significantly. Precise plaque characterization optimizes the choice and evaluation of these percutaneous therapies.

**Limitations**

An inherent limitation of most light-based imaging modalities is the need to achieve a blood-free imaging zone, which in this study was achieved through intermittent saline flushes through the coronary guide catheter. However, even with this flushing technique, the image acquisition time was only a few seconds, which precluded imaging of long arterial segments. As a result, it is possible that we failed to image an exact rupture site or thrombus within a culprit lesion. A further limitation is the relatively shallow axial penetration (2 mm), but because the most important morphological determinants of plaque vulnerability are superficial, the region of greatest interest is within the imaging range of current OCT systems. Enhancements to OCT technology, including improvements in saline delivery, higher penetration depth, and faster acquisition rates, have already been demonstrated. Second-generation OCT systems may allow screening of long coronary segments and eliminate many of the technical limitations of the present study.

**Conclusions**

The resolution of OCT provides histology-grade definition of the microstructure of coronary plaque in vivo and allows a greater understanding of the mechanisms of coronary artery disease. The frequency of thin fibrous cap and TCFA was significantly higher in patients with AMI and ACS compared with those with stable angina. This new technique may provide an opportunity to detect vulnerable plaques before rupture.

**Acknowledgments**

This study was funded in part by the Center for Integration of Medicine and Innovative Technology (development of the imaging platform), the National Institutes of Health (grant R01-HL70039), Guidant Corporation, and a generous gift from Dr and Mrs J.S. Chen to the optical diagnostics program of the MGH Wellman Laboratories for Photomedicine. We thank our research staff at the Cardiovascular Clinical Research and nurses and technologists at the cardiac catheterization laboratories of the Massachusetts General Hospital.
Disclosure

Dr Jang served as a consultant for Guidant Corporation during the time this study was conducted.

References


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Circulation. 2005;111:1551-1555; originally published online March 21, 2005;
doi: 10.1161/01.CIR.0000159354.43778.69

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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