Intravascular Imaging

Coronary Calcification and Plaque Vulnerability
An Optical Coherence Tomographic Study

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Background—Spotty superficial calcium deposits have been implicated in plaque vulnerability based on previous intravascular imaging studies. Biomechanical models suggest that microcalcifications between 5 and 65 μm in diameter can intensify fibrous cap stress, promoting plaque rupture. However, the 100- to 200-μm resolution of intravascular ultrasound limits its ability to discriminate single calcium deposits from clusters of smaller deposits, and a previous optical coherence tomographic investigation evaluated calcifications within a long segment of artery, which may not truly reflect the mechanics involved in potentiating focal plaque rupture.

Methods and Results—Detailed optical coherence tomographic assessment of coronary calcification at the culprit plaque (10-mm length) was performed in 53 patients with acute ST-segment-elevation myocardial infarction mediated by plaque rupture and 55 patients with stable angina pectoris. The number and longitudinal length of individual calcium deposits were recorded. Cross-sectional images were analyzed every 1 mm for calcium arc and depth, and these quantitative parameters were used to define individual deposits as spotty, large, and superficial. There was no significant difference between ST-segment-elevation myocardial infarction mediated by plaque rupture and stable angina pectoris groups in the number of total (P=0.58), spotty (P=0.87), or large calcium deposits (P=0.27). Minimum calcium depth was similar between groups (P=0.27), as was the number of superficial deposits (P=0.35 using a 65-μm depth threshold and P=0.84 using a 100-μm depth threshold).

Conclusions—The number and pattern of culprit plaque calcifications did not differ between patients presenting with ST-segment–elevation myocardial infarction mediated by plaque rupture versus stable angina pectoris. The optical coherence tomographic assessment of coronary calcification may not be a useful marker of local plaque vulnerability as previously suspected.


Key Words: atherosclerosis ■ calcium ■ cross-sectional studies ■ myocardial infarction ■ tomography, optical coherence

The effect of coronary artery calcification on local plaque vulnerability remains unclear. The overall degree of coronary calcification, as visualized on angiography and quantified using coronary computed tomography, has been shown to correlate with total atherosclerotic burden and risk of adverse cardiac events. However, different patterns in the distribution of coronary artery calcium have been reported to convey different effects on plaque stability. Spotty and superficial calcium deposits have been implicated in plaque vulnerability based on previous intravascular ultrasound (IVUS) studies and 1 optical coherence tomographic (OCT) study. Moreover, biomechanical models suggest that microcalcifications can intensify stress in the fibrous cap, promoting plaque rupture. In contrast, large calcium deposits are hypothesized to promote local biomechanical plaque stability, and statin therapy has been shown to accelerate the calcification of atherosclerotic lesions.

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The relatively low resolution of coronary computed tomographic (1 mm) and IVUS (100–200 μm) imaging may limit their ability to discriminate single calcium deposits.
from clusters of multiple smaller deposits. As such, OCT, which has a resolution of 15 to 20 µm, may be a preferred imaging modality for the detailed assessment of coronary calcium. A previous OCT study investigated a potential role for coronary calcifications in plaque vulnerability, identifying a greater prevalence of spotty calcium deposits in patients presenting with acute myocardial infarction (AMI) or unstable angina pectoris (UAP) compared with those presenting with stable angina pectoris (SAP). This OCT investigation, however, evaluated calcifications within a long segment of coronary artery, which may not truly reflect the biomechanics involved in potentiating focal plaque rupture. We, therefore, sought to use OCT to investigate the role of coronary calcium on local plaque vulnerability by performing a detailed assessment of coronary calcification in a limited segment of the culprit artery, comparing the plaques of patients with SAP with those presenting with ST-segment–elevation myocardial infarction mediated by plaque rupture (STEMI-PR).

Methods

Study Population

The STEMI-PR group was extracted from a group of 111 patients who were admitted to Hiroshi University Hospital (Hirosaki, Japan) with STEMI between January 2013 and June 2014, provided written informed consent for the primary percutaneous coronary intervention procedure, and underwent frequency domain OCT imaging of the culprit lesion. STEMI was defined as typical chest pain lasting >20 minutes, ECG showing new ST-segment elevation ≥0.1 mV in at least 2 contiguous limb leads or new left bundle branch block, and cardiac markers (creatine kinase-MB or cardiac troponin T) elevated above the upper reference limit. Exclusion criteria included cardiogenic shock, unsuccessful reperfusion to achieve antegrade flow despite aspiration thrombectomy, inability to advance an intravascular imaging catheter to the culprit lesion, and coronary embolism. The culprit vessel was identified based on stress testing or as the site leading superficial calcium, we used calcium depth thresholds of 65 and 100 µm to define individual deposits as those with length <4 mm and maximal arc <90°, and deposits considered to have a calcium-to-lipid arc of 0° and termed lipid-intermixed deposits. Spotty calcium deposits (Figure 1A) were defined as signal absent (black) holes within a plaque measuring 50 to 300 µm in diameter and visible on at least 3 contiguous OCT frames. For plaques classified as primarily lipid, the lipid arc and minimum fibrous cap thickness were also recorded.

The spatial relationship between lipid pools and calcium deposits was assessed by measuring the smallest arc separating a calcium deposit from a lipid pool on cross-sectional images. Calcium deposits embedded within, adjacent to, or overlying a lipid pool were considered to have a calcium-to-lipid arc of 0° and termed lipid-interfacing deposits. Spotty calcium deposits (Figure 1A) were defined as those with length <4 mm and maximal arc <90°, and deposits not meeting these criteria were classified as large calcium deposits (Figure 1B). Given the lack of established OCT criteria for defining superficial calcium, we used calcium depth thresholds of 65 µm and 100 µm to define individual deposits as superficial-65 and superficial-100, respectively. Calcium deposits were considered distorting if the luminal contour was narrowed or shifted by the shape of the underlying calcium.

Additional plaque characterization was performed according to previously described criteria. Thin-cap fibroatheroma was identified as lipid-rich plaques (lipid arc, >90°) with an overlying minimum fibrous cap thickness of <65 µm. Macrophage accumulations were recognized as linear series of highly reflective (bright) spots with high signal attenuation. Microchannels were defined as signal absent (black) holes within a plaque measuring between 50 and 300 µm in diameter and visible on at least 3 consecutive frames on pullback imaging. Cholesterol crystals were

OCT Image Analysis

OCT image analysis was centered around a designated culprit frame, identified in SAP cases as the cross-sectional image with the minimum lumen area and in STEMI-PR cases as the cross-sectional image at the center of the OCT-identified plaque rupture cavity. In all cases, a 10-mm culprit segment (5 mm proximal to 5 mm distal to the culprit frame) was analyzed. A 30-mm segment (15 mm proximal to 15 mm distal to the culprit frame) was also analyzed in the subset of cases for which these boundaries fell within the 54-mm pullback image length.

Calcium was recognized as heterogeneous areas of high and low reflectivity, with low signal attenuation and a sharply demarcated border. In contrast, lipid was identified as a homogeneous area of low reflectivity with high signal attenuation and a diffuse border. Fibrous tissue was characterized as homogeneous areas of high reflectivity with low signal attenuation. The number and longitudinal length of individual calcium deposits were recorded. Each calcium deposit was categorized as either proximal to, distal to, or spanning the culprit frame. Quantitative analysis was performed using cross-sectional OCT images at 1-mm intervals, and lumen area was measured. Calcium deposits were analyzed individually by measuring calcium arc and depth (minimum distance from lumen to superficial calcium edge). Calcium index was calculated for each calcium deposit as the product of calcium length and mean calcium arc. Total calcium index was calculated as the sum of the calcium index of each calcium deposit within the analyzed vessel segment. The mean calcium index was calculated as the total calcium index divided by the number of calcium deposits. For plaques classified as primarily lipid, the lipid arc and minimum fibrous cap thickness were also recorded.

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OCT Image Acquisition

A frequency domain OCT system (C7-XR OCT Intravascular Imaging System or ILUMIEN OCT Intravascular Imaging System, St. Jude Medical, Saint Paul, MN) was used in all cases. For the STEMI-PR group, 200 mg aspirin, 300 mg clopidogrel, and 100 IU/kg heparin were administered before the procedure, and manual thrombectomy was performed as needed to restore antegrade coronary flow. The OCT imaging catheter was then advanced distal to the lesion, and automated pullback imaging was performed during simultaneous injection of contrast media or dextran through the guiding catheter to clear blood from the imaging field. Thrombectomy was repeated when image quality was suboptimal. All images were deidentified, digitally stored, and submitted to the Massachusetts General Hospital Cardiac Lab for Integrative Physiology and Imaging for offline analysis using proprietary software (LightLab Imaging).
identified as thin linear structures with high reflectivity and low signal attenuation.

**Statistical Analysis**

Categorical variables are presented as counts and percentages, and comparisons were performed using a Fisher exact or $\chi^2$ test. The distribution of continuous variables was evaluated with the Kolmogorov–Smirnov test. We report mean±SD for normally distributed data and median (25th to 75th percentile) for data that are not normally distributed. Comparisons for continuous variables were performed using an independent samples $t$ test or Mann–Whitney $U$ test. All tests were 2-sided, and $P$ values below a threshold of 0.05 were considered to be significant. All statistical analyses were performed using IBM SPSS Statistics 19.0 (SPSS Inc, Chicago, IL).

**Results**

**Patient Characteristics**

A total of 108 plaques were analyzed, including the culprit coronary segments of 55 patients who presented with SAP and 53 patients who presented with STEMI caused by plaque rupture. Baseline demographic and clinical characteristics are summarized and compared as shown in Table 1. Patients in the STEMI-PR group were older and more commonly active smokers than patients in the SAP group. On initial presentation, patients with STEMI-PR were less frequently on aspirin, clopidogrel, $\beta$-blockers, or statins than patients with SAP and had higher total cholesterol and low-density lipoprotein levels.

**Plaque Characteristics**

Quantitative and qualitative plaque characteristics are summarized and compared as shown in Table 2. The minimum luminal area was smaller in the STEMI-PR group compared with the SAP group (1.69±0.73 versus 2.44±1.43 mm$^2$; $P<0.01$). Culprit plaques in the STEMI-PR group had larger mean lipid arcs (240.2±66.2° versus 146.3±76.5°; $P<0.01$) and thinner fibrous caps (68.8±20.9 versus 123.1±55.6 µm; $P<0.01$) and were more frequently categorized as thin-cap fibroatheroma (56.6% versus 18.2%; $P<0.01$), compared with the culprit plaques in the SAP group. The prevalence of microchannels and macrophages was similar between groups, although cholesterol crystals were more frequently seen in the STEMI-PR group compared with the SAP group (77.4% versus 41.8%; $P<0.01$).

**Calcium Analysis**

Detailed OCT analysis of calcium deposits is summarized in Table 3. There was no significant difference between the STEMI-PR and SAP groups in the median number of total

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**Figure 1.** Cross-sectional optical coherence tomography images of calcium. Calcium is identified on optical coherence tomographic images as a heterogeneous area of high and low reflectivity, with low signal attenuation and a sharply demarcated border. **A**, Spotty calcium deposits (arrow) are defined as a deposit with length <4 mm and maximal arc <90°. **B**, Large calcium deposits (arrow) are those with length $\geq$4 mm or maximal arc $\geq$90°. The asterisks denote guidewire shadow artifact.

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**Table 1. Patient Characteristics**

| & STEMI-PR (n=53) & SAP (n=55) & $P$ Value |
|---|---|---|---|
| Age, y | 69.5±13.1 | 63.4±10.0 | <0.01 |
| Male sex (%) | 38 (71.7) | 43 (78.2) | 0.51 |
| BMI, kg/m$^2$ | 24.6±3.64 | 25.9±4.16 | 0.07 |
| Risk factors, % | & | & | & |
| Hypertension | 38 (71.7) | 46 (83.6) | 0.17 |
| Hyperlipidemia | 38 (71.7) | 35 (66.0) | 0.68 |
| Current smoking | 20 (37.7) | 8 (15.4) | 0.02 |
| Diabetes mellitus | 23 (43.4) | 14 (25.5) | 0.07 |
| Previous MI | 2 (3.8) | 9 (16.7) | 0.05 |
| Medications, % | & | & | & |
| Aspirin | 5 (9.4) | 42 (76.4) | <0.01 |
| Clopidogrel | 1 (1.9) | 24 (43.6) | <0.01 |
| Statin | 11 (22.0) | 29 (52.7) | <0.01 |
| $\beta$-blocker | 3 (6.0) | 26 (47.3) | <0.01 |
| ACEi/ARB | 16 (30.2) | 27 (49.1) | 0.05 |
| Labwork, mg/dL | & | & | & |
| Creatinine | 0.88±0.2 | 0.94±0.73 | 0.54 |
| Total cholesterol | 201.5±41.0 | 161.0±39.3 | <0.01 |
| LDL | 128.8±41.4 | 91.0±32.9 | <0.01 |
| HDL | 44.8±10.4 | 45.4±16.9 | 0.85 |
| Triglycerides | 139.4±137.2 | 127.8±59.4 | 0.60 |

Data are presented as mean±SD or n (%). ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction; SAP, stable angina pectoris; and STEMI-PR, ST-segment-elevation myocardial infarction plaque rupture.
calcium deposits ($P=0.58$), spotty calcium deposits ($P=0.87$), or large calcium deposits ($P=0.27$). The total calcium index and mean calcium index were also similar between groups ($P=0.31$ and $P=0.11$, respectively). There was no significant difference in the minimum calcium depth ($P=0.27$), the number of superficial-65 deposits ($P=0.35$), or the number of superficial-100 deposits ($P=0.84$) between the STEMI-PR and SAP groups. Moreover, the number of calcium deposits that were both spotty and superficial-65 or both spotty and superficial-100 was also similar between the STEMI-PR and SAP groups ($P=0.96$ and $P=0.71$, respectively). The number of lipid-interfacing calcium deposits was similar between the STEMI-PR and SAP groups ($P=0.65$). There was also no significant difference in the number of lipid-interfacing calcium deposits that were also spotty ($P=0.28$), spotty and superficial-65 ($P=0.26$), or spotty and superficial-100 ($P=0.21$).

Thirty-Millimeter Segment Analysis
Among the 108 cases included in this study, 70 cases (36 STEMI-PR and 34 SAP) had OCT imaging that enabled analysis of calcifications within a 30-mm segment (from 15 mm proximal to 15 mm distal) spanning the culprit frame. Detailed 30-mm segment OCT analysis of calcium deposits in this subgroup of patients is summarized in Table 4. There was a trend toward a higher number of total calcium deposits ($P=0.08$) and spotty calcium deposits ($P=0.06$) in the STEMI-PR group compared with the SAP group, although this did not reach statistical significance. There was no difference between groups in the number of deposits that were classified as large ($P=0.66$), superficial-65 ($P=0.60$), superficial-100 ($P=0.42$), both spotty and superficial-65 ($P=0.72$), or both spotty and superficial-100 ($P=0.59$).

Discussion
Extracellular calcium deposits have long been recognized as a prominent feature in the development and progression of atherosclerosis. Coronary artery calcification is associated with advanced atherosclerosis and increased risk of adverse cardiac events. However, the specific effect of calcium deposits

<table>
<thead>
<tr>
<th>Table 2. Plaque Characteristics</th>
<th>STEMI-PR (n=53)</th>
<th>SAP (n=55)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum luminal area, mm$^2$</td>
<td>1.69±0.73</td>
<td>2.44±1.43</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean lipid arc, °</td>
<td>240.2±66.2</td>
<td>146.3±76.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Minimum FCT, µm</td>
<td>68.8±20.9</td>
<td>123.1±55.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>TCFA (%)</td>
<td>30 (56.6)</td>
<td>10 (18.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Macrophages (%)</td>
<td>50 (94.3)</td>
<td>45 (81.8)</td>
<td>0.07</td>
</tr>
<tr>
<td>Microchannels (%)</td>
<td>17 (32.1)</td>
<td>20 (36.4)</td>
<td>0.69</td>
</tr>
<tr>
<td>Cholesterol crystals (%)</td>
<td>41 (77.4)</td>
<td>23 (41.8)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD or n (%). FCT indicates fibrous cap thickness; SAP, stable angina pectoris; STEMI-PR, ST-segment–elevation myocardial infarction plaque rupture; and TCFA, thin-cap fibroatheroma.

<table>
<thead>
<tr>
<th>Table 3. Optical Coherence Tomography Calcium Analysis</th>
<th>STEMI-PR (n=53)</th>
<th>SAP (n=55)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total calcium deposits</td>
<td>1 (0–2.5)</td>
<td>1 (0–3)</td>
<td>0.58</td>
</tr>
<tr>
<td>Spotty calcium</td>
<td>1 (0–2)</td>
<td>1 (0–2)</td>
<td>0.87</td>
</tr>
<tr>
<td>Large calcium</td>
<td>0 (0–1)</td>
<td>0 (0–1)</td>
<td>0.27</td>
</tr>
<tr>
<td>Total calcium index</td>
<td>242.3±282.6</td>
<td>317.1±324.5</td>
<td>0.31</td>
</tr>
<tr>
<td>Mean calcium index</td>
<td>92.8±96.1</td>
<td>146.9±173.7</td>
<td>0.11</td>
</tr>
<tr>
<td>Minimum calcium depth, µm</td>
<td>111.5±97.1</td>
<td>84.7±103.0</td>
<td>0.27</td>
</tr>
<tr>
<td>Superficial-65</td>
<td>0 (0–1)</td>
<td>0 (0–1)</td>
<td>0.35</td>
</tr>
<tr>
<td>Superficial-100</td>
<td>0 (0–1)</td>
<td>0 (0–1)</td>
<td>0.84</td>
</tr>
<tr>
<td>Spotty and superficial-65</td>
<td>0 (0–0)</td>
<td>0 (0–0)</td>
<td>0.96</td>
</tr>
<tr>
<td>Spotty and superficial-100</td>
<td>1 (0–1)</td>
<td>0 (0–1)</td>
<td>0.71</td>
</tr>
<tr>
<td>Lipid interfacing</td>
<td>1 (0–2)</td>
<td>1 (0–2)</td>
<td>0.65</td>
</tr>
<tr>
<td>Lipid interfacing and spotty</td>
<td>1 (0–1)</td>
<td>0 (0–1)</td>
<td>0.28</td>
</tr>
<tr>
<td>Lipid interfacing and spotty and superficial-65</td>
<td>0 (0–0)</td>
<td>0 (0–0)</td>
<td>0.26</td>
</tr>
<tr>
<td>Lipid interfacing and spotty and superficial-100</td>
<td>0 (0–1)</td>
<td>0 (0–0)</td>
<td>0.21</td>
</tr>
<tr>
<td>Proximal to culprit frame</td>
<td>0 (0–1)</td>
<td>0 (0–1)</td>
<td>0.44</td>
</tr>
<tr>
<td>Distal to culprit frame</td>
<td>0 (0–1)</td>
<td>0 (0–1)</td>
<td>0.45</td>
</tr>
<tr>
<td>Spanning culprit frame</td>
<td>0 (0–1)</td>
<td>0 (0–0)</td>
<td>0.07</td>
</tr>
<tr>
<td>Distorting</td>
<td>0 (0–1)</td>
<td>0 (0–0)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Data are presented as median (interquartile range) or mean±SD or n (%). SAP indicates stable angina pectoris; and STEMI-PR, ST-segment–elevation myocardial infarction plaque rupture.
on local plaque vulnerability remains unclear. Computed tomographic studies demonstrated a correlation between a spotty pattern of calcification (<3 mm) and presentation with acute coronary presentations. Early pathological studies, however, suggest that although the degree of calcification is an excellent marker for plaque burden, it correlates poorly with luminal narrowing and may not affect the biomechanical stability of atherosclerotic plaques.

Intravascular imaging can be performed in vivo to further elucidate the potential role of calcium in plaque vulnerability. In this study, we did not identify a significant difference in the number or pattern of culprit lesion OCT-identified coronary calcium deposits between patients with SAP and STEMI-PR, 2 extremes of clinical presentation. Our findings are in distinct contrast to several IVUS and 1 previous OCT study, which have suggested that spotty and superficial calcium deposits may increase local plaque vulnerability. We think that this difference derives from inherent limitations to IVUS imaging and important methodological dissimilarities between the previous studies and our current investigation.

**IVUS Studies of Coronary Artery Calcium**

In an early IVUS study by Beckman et al., the relationship between culprit coronary artery calcification and clinical presentation was explored in 78 patients. The maximal arc of calcium within the stented segment and the mean of the calcium arcs measured at the proximal, middle, and distal stented segments increased progressively for the groups of patients with AMI, UAP, and SAP, suggesting that smaller calcium deposits may contribute to unstable clinical presentations. Calcium measurements, however, were only taken from 4 frames within the stented segment, and it is possible that the stented vessel lengths analyzed in this study differed between groups.

A subsequent IVUS study analyzed culprit lesion images obtained before intervention and included 178 patients (47 with SAP, 70 with UAP, and 61 with AMI). The number of spotty calcium deposits was significantly higher in the AMI compared with the SAP group, and the average length of each calcium deposit was smaller in the AMI and UAP groups compared with the SAP group. Calcium analysis was restricted to the 10-mm-long culprit segment (5 mm proximal to 5 mm distal to the culprit lesion frame). The mean number of calcium deposit in the AMI group was 1.4, which is similar to what we found in our study for the STEMI-PR group. The mean number of calcium deposits in the SAP group, however, was 0.5 in the IVUS study, compared with 1.67 in our study. One possible explanation for these discrepant findings is that a single large calcium deposit visualized using IVUS may actually represent multiple smaller calcium deposits that can be distinguished pathologically or with higher-resolution OCT imaging. Figure 2 shows cross-sectional OCT images with multiple calcifications that may seem as a single deposit on lower resolution imaging.

In a study of pooled data from 7 clinical IVUS trials, 1347 patients with stable angina were grouped according to the presence or absence of spotty calcification (arc, <90°). The group with spotty calcification had a greater percent atheroma volume and total atheroma volume at baseline, as well as greater progression of percent atheroma volume on serial evaluation. The authors concluded that spotty calcification was associated with more extensive and diffuse coronary atherosclerosis and accelerated disease progression. Importantly, however,
this study evaluated nonculprit vessels, and the study findings may, therefore, not be applicable to the investigation of plaque vulnerability.

Superficial calcifications, in contrast to deep calcifications, have also been implicated in plaque vulnerability. On IVUS imaging, calcium has been defined as superficial if the leading edge of acoustic shadowing seemed within the shallowest 50% of the plaque plus media and deep if it seemed within the deeper 50% of the plaque plus media thickness.\(^2\) A study comparing 101 IVUS-detected ruptured plaques with 101 matched controls found that a significantly larger number of calcium deposits in ruptured versus control plaques; however, this difference was driven by deep calcium deposits, as there was no difference in the number of superficial calcium deposits between groups.\(^2\)

Although IVUS has been shown to be highly sensitive and specific for the identification of calcified plaque, its accuracy in the quantitative assessment of calcium, particularly variability in the measured arc of calcium, has been questioned.\(^2\) In a study using ex vivo coronary arteries, OCT-derived calcium measurements correlated better with histological examination than IVUS-derived measurements.\(^2\) Excellent correlation in the measurement of calcium depth and angle has been shown between OCT-imaged and cryo-imaged cadaveric coronary samples.\(^2\)

**OCT Study of Coronary Artery Calcium**

To the best of our knowledge, only 1 previous study has used OCT to evaluate the potential role of coronary calcium in plaque vulnerability. In a study of 187 consecutive patients (44 with AMI, 73 with UAP, and 70 with SAP) with coronary artery disease who underwent culprit lesion OCT imaging, Mizukoshi et al.\(^4\) found that the arc, length, and area of calcium were significantly smaller in patients presenting with AMI and UAP compared with those presenting with SAP (\(P<0.01\)). Spotty calcifications with an arc of \(<90^\circ\) were significantly more prevalent in the AMI and UAP groups than in the SAP group (\(P<0.01\)), whereas large calcium deposits with an arc of \(>90^\circ\) were significantly more prevalent in the SAP group than in the AMI and UAP groups (\(P<0.01\)). Moreover, the calcifications in the AMI and UAP groups were more superficial than those in the SAP group (\(P<0.01\)). The authors hypothesized that spotty and superficial calcifications might, therefore, play a role in plaque vulnerability.\(^1\) Importantly, however, a 30-mm segment spanning from 15 mm proximal to 15 mm distal to the culprit site was used for the assessment of plaque morphology. Calcium deposits remote from a culprit rupture site are unlikely to biomechanically contribute to focal risk of rupture, and a previous study suggests that the culprit lesions of patients with acute coronary syndrome are, on average, only \(\approx16\) mm in length.\(^26\) We, therefore, focused our OCT calcium analysis to a 10-mm culprit segment and found no significant difference in the number or pattern of calcium deposits between patients presenting with SAP and STEMI-PR. Interestingly, in the subset of patients in whom culprit lesion OCT images enabled a full 30-mm segment analysis, we found a trend toward a higher number of total and spotty calcium deposits in the STEMI-PR group than in the SAP group, which is consistent with the findings from the study by Mizukoshi et al.\(^4\)

**Mathematical Models**

Mathematical models investigating the biomechanical effect of calcifications within a fibrous cap support the hypothesis that single microcalcifications\(^27\) and clusters of microcalcifications\(^28\) increase local tissue stress, thereby promoting vulnerability for rupture. These models are frequently cited as supportive evidence for the conclusions drawn by these previous intravascular imaging studies. Importantly, however, the mathematical models emphasize a critical microcalcification size between 5 and 65 \(\mu\)m, outside of which microcalcifications should not be biomechanically dangerous.\(^29\) Calcium deposits of this size are below the resolution of IVUS imaging and challenging to identify on OCT imaging. Although the resolution of OCT imaging is 15 to 20 \(\mu\)m, in our experience, calcium deposits must be several times larger than that to be confidently identified using the defining OCT features of heterogeneous reflectivity with low signal attenuation and a sharply demarcated border. Our findings do not suggest a direct role for OCT-identified coronary calcium, spotty calcium, or superficial calcium in promoting plaque vulnerability for rupture. Rather, as suggested in early pathological studies, coronary calcium may be more reflective of total atherosclerotic risk than local biomechanical instability.

Interestingly, we identified a trend toward a greater number of calcifications spanning the culprit frame and a greater median number of calcium deposits distorting the lumen in patients presenting with SAP than STEMI-PR. One potential explanation for this result is that distorting calcifications occur when calcium deposits form without adequate compensatory positive remodeling. These deposits, therefore, contribute to focal luminal narrowing that, if severe enough, can become a culprit minimum lumen area site that manifests clinically as SAP. Indeed, large plaque burden and small lumen area have been shown to be useful morphological features for discriminating plaques that manifest as culprit lesions from those that remain clinically silent.\(^30\)

**Limitations**

There are several limitations to our study that merit acknowledgment. First, the study population was small, including 108 patients totally (55 with SAP and 53 with STEMI-PR). Second, OCT imaging was performed at the discretion of the operator, introducing potential selection bias. Third, the differentiation of lipid pools from calcium deposits on OCT imaging can be challenging. However, the sharply demarcated border of calcium, in comparison with the scattered border of lipid, has been used as an important distinguishing characteristic.\(^31\) In addition, algorithms are under development for more objective and automated OCT-identification of calcium.\(^32,33\) Fourth, residual thrombus, particularly in the STEMI-PR group, may have limited the identification of underlying calcium deposits. We, therefore, excluded cases with poor OCT image quality, including cases with excessive residual thrombus. It is possible that specific patterns of...
plaque calcification may be associated with greater thrombogenicity, and the exclusion of these cases may, therefore, have influenced our results.

Conclusions
In contrast to previous IVUS and OCT studies, we found no significant difference in the number or pattern of culprit segment calcium deposits between patients presenting with SAP and STEMI-PR. This discrepancy may be derived from the limited resolution of IVUS imaging and important methodological differences between this and previous intravascular imaging studies. Coronary calcification, as assessed by OCT, may not be a useful marker of local plaque vulnerability as previously suspected.

Disclosures
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References


**CLINICAL PERSPECTIVE**

Despite improvements in stent technology, implantation techniques, and adjunctive medical therapy, the risk of recurrent cardiac events after successful percutaneous coronary intervention remains high. The identification of vulnerable plaques at high risk for evolving into culprit plaques, therefore, remains an active area of investigation. Intravascular imaging has facilitated the identification of multiple morphological features associated with plaque vulnerability, and previous studies have suggested that spotty superficial calcium deposits may be a marker of increased plaque vulnerability. These studies, however, had methodological limitations. In this study, we performed a detailed assessment of culprit lesion coronary calcification using optical coherence tomography. We found no significant difference in the number or pattern of calcium deposits between patients who presented with ST-segment–elevation myocardial infarction mediated by plaque rupture versus patients who presented with stable angina. Our findings suggest that coronary calcification, as assessed using optical coherence tomography, may not be a useful marker of local plaque vulnerability as previously suspected.
Coronary Calcification and Plaque Vulnerability: An Optical Coherence Tomographic Study
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Supplemental figure 1: Consort diagram for the STEMI-PR study cohort

STEMI-PR group

111 patients
- STEMI presentation between January 2013 and June 2014
- FD-OCT imaging of culprit lesion

72 patients
- Plaque erosion (30)
- Calcified nodule (9)

53 cases included for 10-mm analysis
- Poor image quality (19)

36 patients included for 30-mm analysis
- Culprit too proximal/distal for full 30-mm vessel segment analysis (17)

STEMI-PR: ST elevation myocardial infarction caused by plaque rupture; FD-OCT: frequency domain optical coherence tomography
Supplemental figure 2: Consort diagram for the SAP study cohort

**SAP group**

613 patients
- SAP presentation between August 2010 and May 2014
- FD-OCT imaging of culprit lesion

- No pre-intervention OCT imaging (536)
- Poor OCT image quality (14)
- Culprit too proximal/distal for full 10-mm vessel segment analysis (8)

55 patients included for 10-mm analysis

- Culprit too proximal/distal for full 30-mm vessel segment analysis (21)

34 cases included for 30-mm analysis

SAP: stable angina pectoris; FD-OCT: frequency domain optical coherence tomography