Spotty Calcification Typifies the Culprit Plaque in Patients With Acute Myocardial Infarction
An Intravascular Ultrasound Study

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Background—Calcification is a common finding in human coronary arteries; however, the relationship between calcification patterns, plaque morphology, and patterns of remodeling of culprit lesions in a comparison of patients with acute coronary syndromes (ACS) and those with stable conditions has not been documented.

Methods and Results—Preinterventional intravascular ultrasound (IVUS) images of 178 patients were studied, 61 with acute myocardial infarction (AMI), 70 with unstable angina pectoris (UAP), and 47 with stable angina pectoris (SAP). The frequency of calcium deposits within an arc of less than 90° for all calcium deposits was significantly different in culprit lesions of patients with AMI, UAP, and SAP ($P < 0.0001$). Moreover, the average number of calcium deposits within an arc of $<90°$ per patient was significantly higher in AMI than in SAP ($P < 0.0005$; mean $\pm$ SD, AMI 1.4 $\pm$ 1.3, SAP 0.5 $\pm$ 0.8). Conversely, calcium deposits were significantly longer in SAP patients ($P < 0.0001$; mean $\pm$ SD, AMI 2.2 $\pm$ 1.6, UAP 1.9 $\pm$ 1.8, and SAP 4.3 $\pm$ 3.2 mm). In AMI patients, the typical pattern was spotty calcification, associated with a fibrofatty plaque and positive remodeling. In ACS patients showing negative remodeling, no calcification was the most frequent observation. Conversely, SAP patients had the highest frequency of extensive calcification.

Conclusions—Our observations show that IVUS allows the identification of vulnerable plaques in coronary arteries, not only by identifying a fibrofatty plaque and positive remodeling, but also by identifying a spotty pattern of calcification.

Key Words: coronary disease ■ remodeling ■ ultrasonics ■ calcium ■ myocardial infarction

Atherosclerotic plaque calcification is a common phenomenon, well known to pathologists and usually associated with long-standing atherosclerotic disease; however, the clinical relevance of this phenomenon (for instance, as a risk factor for plaque vulnerability) is still controversial. Histopathological studies have shown unequivocally that vulnerable atherosclerotic plaques contain calcific deposits, although the extent and radiographic appearance of the calcifications varied considerably.1,2

Recently, histopathological findings became clinically relevant with the introduction of electron-beam computed tomography (EBCT), which enables the quantitative assessment of coronary artery calcifications. Raggi et al3 reported that the amount of coronary calcium detected by EBCT is similar in patients with unstable angina pectoris (UAP) versus those with stable angina pectoris (SAP); however, a recent report by Beckman et al4 demonstrated that culprit lesions in SAP patients are more extensively calcified than those in UAP patients and are least calcified in AMI patients. IVUS studies, moreover, revealed that positive remodeling (PR) is associated with acute coronary syndromes (ACS), whereas negative remodeling (NR) is more common in SAP patients.6–8
Thus far, to the best of our knowledge, no IVUS studies have been reported that document the association between arterial remodeling, patterns of coronary calcification, and morphology of atherosclerotic plaques at the site of culprit lesions in patients with AMI, UAP, or SAP. The present study has been designed for this purpose.

Methods
The study was approved by the hospital ethics committee, and informed consent was obtained from all patients before the study.

Patients
Preinterventional IVUS images were obtained of 199 consecutive patients with either AMI, UAP, or SAP. In all patients, the procedure was performed on a native de novo atherosclerotic lesion that was considered to be the culprit lesion. Twenty-one patients were excluded from analysis for technical reasons; in 18 patients, the images could not be analyzed because of poor image quality, and severe calcification precluded accurate measurement of vessel size in 3 patients (all 3 with SAP).

The study population, therefore, contained 178 patients with either AMI, UAP, or SAP. There were 61 patients with AMI. The diagnosis was based on a history of prolonged ischemic chest pain, characteristic ECG changes, and elevated creatine kinase (>2 times above normal range) within 24 hours after the onset of pain. UAP was diagnosed in 70 patients. UAP was defined either as new-onset angina within 2 months after a previous bout, angina with a progressive crescendo pattern (with anginal episodes increasing in frequency or duration), angina that occurred at rest, or angina that occurred in the immediate postinfarction period. Patients with UAP were further divided into class I (n=33), class II (n=9), and class III (n=28), according to Braunwald’s criteria. At the time of the study, troponin levels were not determined. SAP was diagnosed in another 47 patients and defined as chest pain typical of cardiac ischemia on exertion.

IVUS Imaging
IVUS imaging was performed before intervention and only after administration of 0.2 mg of intracoronary nitroglycerin. Studies were performed with a commercially available system (Boston Scientific Corporation/Cardiovascular Imaging Systems Inc, with a 30-MHz transducer). The IVUS catheter was carefully advanced distal to the culprit lesion under fluoroscopic guidance, and it was then withdrawn automatically at 0.5 mm/s to perform the imaging sequence, which started 20 mm distal to the culprit lesion and ended at the aorto-ostial junction. Repeated injections of saline solution were performed to facilitate identification of the lumen. IVUS studies were recorded on super-VHS videotape for offline analysis.

IVUS Analysis
Quantitative measurements were obtained offline with a computer-assisted IVUS analysis system (Tape Measure, Indec Systems Inc) by a single experienced observer (Y.K.) who was unaware of the clinical data.

Dimensional Measurements
The culprit lesion site and a proximal reference site were selected for measurement. The culprit vessel was identified on the basis of clinical, ECG, and angiographic data. In SAP patients, the culprit vessel was considered to be the ischemia-related vessel identified by exercise scintigram stress test. The culprit lesion site selected for analysis was the image slice with the smallest lumen cross-sectional area (CSA); if there were several image slices with an equally small lumen CSA, the image slice with the largest external elastic membrane (EEM) CSA and plaque CSA was selected for analysis. When acoustic shadowing in the culprit image slice made identification of the EEM difficult, 2 types of extrapolation methods were used, according to the method described previously. The proximal reference site was chosen as the image slice with the least amount of plaque, within 15 mm proximal to the culprit lesion site without any intervening side branch. At each culprit lesion and each proximal reference site, EEM CSA and lumen CSA were manually traced. Plaque CSA was calculated as EEM CSA minus lumen CSA. Percent plaque area was calculated as (plaque CSA/EEM CSA)×100 (%).

Definition of Arterial Remodeling
The remodeling index was defined as the ratio of the EEM CSA at the culprit lesion site to the EEM CSA at the proximal reference site. Three remodeling categories were defined: PR, a remodeling index >1.05; NR, a remodeling index <0.95; and intermediate remodeling (IR), a remodeling index between 0.95 and 1.05.

Quantitative Assessment of Culprit Lesion Calcification
Calcium was defined by the presence of a bright echogenic signal with acoustic shadowing. The 10-mm-long culprit lesion segment (5 mm proximal and 5 mm distal to the culprit lesion site) was used for assessment of calcification according to previous reports.

In each of the 178 patients, the presence and extent of calcium within the 10-mm-long segment were quantified with 20 serial cross-sectional IVUS images, obtained every second, which corresponded to images 0.5 mm apart, according to the method described by Scott et al. In each patient, the arc of each calcium deposit observed in each of the 20 serial IVUS images was measured with a protractor centered on the lumen, and then the largest arc of each calcium deposit within the 10-mm-long segment was identified. In addition, in each patient, the number of calcific deposits and the length of each calcium deposit in the 10-mm-long segment were calculated with 20 serial cross-sectional images. Intraobserver analysis was performed by the same observer (Y.K.) at least 2 weeks apart. Interoobserver differences in measurement of the arc of calcium were 3.4±2.2%.

Patterns of Culprit Lesion Calcification
In each patient, based on the outcome of the quantification of coronary calcium deposits, the 10-mm-long culprit lesion segment was categorized into 1 of 4 groups: (1) no calcification: a lesion in which calcium was not detected; (2) spotty calcification: a lesion that contained only small calcium deposits within an arc of less than 90°; (3) intermediate calcification: a moderate calcific lesion with an arc of 90° to 180° in >1 cross-sectional image of the lesion; and (4) extensive calcification: an extensive calcific lesion with an arc of more than 180° in >1 cross-sectional image of the lesion. Assessment of the reproducibility of detecting patterns of culprit lesion calcification was performed in a random sample of 40 patients; the interobserver variability for measurement of the arc of calcium, obtained by 2 independent experienced observers (Y.K., H. Yamashita), was 3.8±2.3%, and the interobserver agreement for patterns of culprit lesion calcification, based on the outcome of the quantification of...
coronary calcium deposits and subsequent categorization into 1 of 4
groups, was 95% (κ=0.93).

Relationship Between IVUS Echodensity and
Plaque Morphology

In both the no calcification and spotty calcification types, plaque
morphology at the site of the culprit lesion segment was visually
assessed independently by 2 observers (Y.K., H. Yamashita), both of
whom were blinded to the clinical data. In cases of disagreement,
consensus was reached by further joint reading. Plaque morphology
was divided into 3 types:11 (1) fibrofatty plaques, defined as lesions
with an echodensity less than that of the adventitia for >70% of the
plaque in an integrated pullback through the lesion; (2) fibrous
plaques in which the echodensity was equivalent to or greater than
that of the adventitia for >70% of the plaque; and (3) mixed plaques,
declared as a mixture of fibrofatty and fibrous components, with each
component occupying <70% of the plaque. In both the intermediate
calcification and extensive calcification types, it was not possible to
reliably assess plaque morphology at the site of the culprit lesion
segment because of extensive acoustic shadowing.12

Statistical Analysis

Results are expressed as mean±SD. In case the data were normally
distributed, the 2 groups were compared with an unpaired t test;
otherwise, a Mann-Whitney U test was used. Statistical comparisons
between more than 3 groups were performed by 1-way ANOVA and
post hoc multiple comparison with Scheffé’s test. Categorical vari-
ables were compared by use of χ² test. Multivariate logistic regres-
sion analysis was performed to identify independent predictors of the
spotty calcification pattern. Values of P<0.05 were considered
significant.

Results

Patient Characteristics

Clinical characteristics of all 178 patients are shown in Table
1. There were no statistically significant differences in age,
gender, presence of risk factors, and culprit vessel among
patients with either AMI, UAP, or SAP.

Calcifications

Characteristics of Each Calcification

As shown in Figure 1, the frequency of calcium deposits
within an arc of <90° for all calcium deposits was signifi-
cantly different in culprit lesions of patients with AMI, UAP,
and SAP (P<0.0001). Figure 1 also shows that the average
number of calcium deposits within an arc of <90° per patient
in AMI was significantly higher than in SAP (mean±SD,
AMI 1.4±1.3, UAP 1.0±1.1, and SAP 0.5±0.8, P<0.0005;
AMI versus SAP, P<0.0005). The average length of each
calcium deposit in patients with either AMI or UAP was
significantly smaller than in SAP (AMI 2.2±1.6, UAP 1.9±1.8, and SAP 4.3±3.2 mm, P<0.0001; AMI versus SAP, P<0.0001, and UAP versus SAP, P<0.0001). In UAP patients, no significant difference existed in size, number, and length of the calcium deposits among the 3 categories of Braunwald’s classification.

Figure 2 shows the arc distribution of each calcification in all patients with calcium deposits in detail. Sixty-one AMI patients had 104 calcifications, 70 UAP patients had 82, and 47 SAP patients had 50.

Calcification Pattern and Plaque Morphology
The relationship between calcification patterns and clinical presentation was assessed in the 3 groups (AMI, UAP, and SAP; Table 2). The frequency of the pattern of culprit lesion calcification was significantly different (P<0.0001). In AMI patients, spotty calcification was the most frequent (51%). In UAP patients, the frequencies of no calcification and spotty calcification were nearly equal. Conversely, in SAP patients, the frequency of extensive calcification was the highest (38%).

The relationship between calcification and plaque morphology among AMI, UAP, and SAP is shown in Table 3. Because plaque morphology could not be reliably identified in cases with intermediate or extensive calcification because of acoustic shadowing, the assessment was based on 128 target segments (AMI, n=47; UAP, n=57; and SAP, n=24).

In AMI patients, spotty calcification with a fibrofatty plaque was the most frequent observation. In UAP, the frequency of no calcification with a fibrofatty plaque was the highest.

<table>
<thead>
<tr>
<th>Pattern of Calcification/Plaque Morphology</th>
<th>AMI (n=47)</th>
<th>UAP (n=57)</th>
<th>SAP (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No calcification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrofatty</td>
<td>11 (23)</td>
<td>24 (42)</td>
<td>6 (25)</td>
</tr>
<tr>
<td>Fibrous</td>
<td>4 (9)</td>
<td>5 (9)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Mixed</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Spotty calcification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrofatty</td>
<td>24 (51)</td>
<td>20 (35)</td>
<td>4 (17)</td>
</tr>
<tr>
<td>Fibrous</td>
<td>4 (9)</td>
<td>4 (7)</td>
<td>8 (33)</td>
</tr>
<tr>
<td>Mixed</td>
<td>3 (6)</td>
<td>4 (7)</td>
<td>2 (8)</td>
</tr>
</tbody>
</table>

Values are n (%).

Table 2. Pattern of Calcification in AMI, UAP, and SAP

Table 3. Relationship Between Calcification and Plaque Morphology

Table 4. IVUS Measurements

Remodeling and Calcification
Twenty-five patients in whom no proximal reference site could be defined because the lesion involved the ostium or a bifurcation were excluded from remodeling analysis. Table 4 shows quantitative IVUS measurements. At the proximal reference site, there were no significant differences between AMI and UAP, on the one hand, and SAP with respect to lumen area, plaque area, EEM area, or percent of plaque area. At the lesion site, lumen area was similar among the 3 groups; however, plaque area, EEM area, and percent plaque area in AMI were significantly larger than in UAP or SAP.

In AMI (n=56), 27 patients (48%) showed PR on IVUS, whereas NR was observed in 15 patients (27%). The remaining 14 patients (25%) showed IR. UAP (n=55) included 17 patients (31%) with PR, 26 (47%) with NR, and 12 (22%) with IR. On the other hand, SAP (n=42) included 9 patients (21%) with PR, 27 (64%) with NR, and 6 (14%) with IR. The frequency of the remodeling categories was significantly different among the 3 groups (P<0.01).

Table 5 shows the relationship between calcification patterns and remodeling in the 9 groups. In AMI and UAP patients with PR, spotty calcification was the most frequent observation (AMI 67%, UAP 47%) compared with no calcification in AMI and UAP patients with NR (AMI 47%, UAP 58%). Conversely, in SAP patients with PR and NR, the frequency of extensive calcification was the highest (PR 44%, NR 41%). Furthermore, in AMI and UAP patients with PR, spotty calcification with a fibrofatty plaque was the most frequent pattern (AMI 79%, UAP 55%).

To identify independent predictors of the spotty calcification pattern, a multivariate logistic regression analysis was performed with age, gender, AMI, UAP, and PR. Multivariate analysis revealed that AMI and PR were independent predictive factors of the spotty calcification pattern (AMI OR 2.9, 95% CI 1.18 to 7.02, P<0.05, PR OR 2.1, 95% CI 1.03 to 4.49, P<0.05). A typical example of spotty calcification with a fibrofatty plaque in AMI with PR is shown in Figure 3.
Discussion

To the best of our knowledge, the present IVUS study is the first to demonstrate the relationship between calcification patterns, arterial remodeling, and the morphology of plaques within the culprit lesion segment. The major finding is that there is a significant difference in the pattern of coronary calcifications at the culprit lesion segment, particularly with respect to size, number, and length of the deposits, among patients with AMI, UAP, and SAP. Small calcium deposits were significantly more frequent in the culprit lesion segments in ACS than in SAP patients. In fact, our qualitative analysis of calcifications demonstrated that the culprit segments of AMI patients were mostly characterized by small calcium deposits, associated with fibrofatty plaques and PR.

Thus far, there have been few quantitative IVUS studies of coronary plaque calcification in lesions associated with ACS. Nakamura et al. recently reported that lesser degrees of calcium were observed in the culprit lesions of ACS patients compared with lesions of patients with stable coronary artery disease. More recently, Beckman et al. demonstrated less calcification in ACS lesions than in SAP by measuring the arc of calcium in IVUS images; however, they examined culprit lesions after placement of a stent, and therefore, arterial remodeling and plaque tissue morphology at the culprit site could not be analyzed. Nevertheless, these previous IVUS data, together with our present findings based on both quantitative and qualitative IVUS analysis, support the conclusion that the pattern of calcium deposits in culprit coronary lesions is different in ACS patients than in SAP patients. The IVUS observations in the present study are endorsed further by a recent study by Shemesh et al. using double helical computerized tomography, which showed that a first AMI most often occurs in mildly calcified or noncalcified culprit arteries, whereas extensive calcifications characterize the coronary arteries of SAP patients. In this context, in the study by Shemesh et al., the term “spotty” refers to calcium deposits that are limited in size, whereas in the present IVUS study, the term has been slightly expanded by referring to small calcium deposits within an arc of <90°.

The present study also revealed a positive relationship in AMI patients between scattered spotty calcifications, the presence of a fibrofatty plaque, and PR of the culprit arterial segment. Furthermore, the present multivariate analysis demonstrated that AMI and PR were independent predictive factors of the spotty calcification pattern. Previous studies have shown that PR is associated with a vulnerable plaque in AMI patients. A pathological study by Burke et al. demonstrated that inflammation, calcification, and medial thinning are the primary determinants of PR. The present IVUS data support these previous data.

What is the clinical relevance of identifying plaque calcification in human atherosclerotic lesions? There is accumulating evidence that atherosclerotic disease is a chronic inflammatory process with involvement of many arterial segments, despite the fact that a single localized culprit lesion may cause an acute syndrome. The likelihood of additional vulnerable segments is a matter of growing concern, because it raises the question whether an interventional procedure directed to one lesion should not tackle others as well. The problem, of course, is to identify such additional vulnerable sites. IVUS is a useful tool for investigating plaque characteristics, and the present observations could be of help in differentiating stable from unstable sites.

The present study has some limitations. Classification of culprit lesions as PR, IR, and NR is somewhat definition dependent. In addition, it is possible that the proximal reference site has already undergone arterial remodeling, and this may affect the assessment of remodeling at the culprit lesion site. The diagnosis of thrombus by IVUS is generally based on presumptive evidence. Therefore, we cannot ex-
clude the possibility that in some lesions, thrombosis may have been present, being indistinguishable from the superficial parts of the culprit plaque; however, it is unlikely that the presence of such thrombus has affected measurement of the vessel area with an appreciable impact on the present results.

Extensive calcifications are likely to be associated with fibrous atherosclerotic segments, whereas small calcium deposits may raise suspicion, certainly when associated with a lipid-rich plaque and PR. It is not the identification of calcium per se that counts but rather the size and extent of the deposits. This refinement in judgment and interpretation of calcifications provides incremental value to IVUS evaluation of arterial segments.

References
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