Quantification of Coronary Calcification by Intravascular Ultrasound
—— Do Calcium Deposits With Larger Arcs Have Longer Lengths? ——

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Background  Previous intravascular ultrasound (IVUS) studies have shown that calcification can be quantified by the determination of the arc on one cross-section. However, because calcium levels change along the length of lesions, it is important to assess the length of calcium using serial cross-sectional images. The correlation between the largest arc and length of each calcium deposit in patients with coronary artery disease (CAD) has not been determined. The present study was performed to determine this correlation.

Methods and Results  Preinterventional IVUS images of 194 patients with CAD were studied. The largest arc and length of all calcium within the 10-mm-long culprit lesion segment were quantified using serial cross-sectional images. One hundred and ninety-four patients had 277 calcium deposits. In all patients, the length of each calcium exhibited a strong correlation with the largest arc of calcium (R=0.750, p<0.0001).

Conclusions  Our findings revealed the quantitative characteristics of each calcium within the culprit lesion segment. They will be useful in interpreting results of previous and future IVUS studies, which deal only with the arc of calcium, as well as studies using new modalities such as computed tomography that assess calcium mainly along the long axis of the coronary artery. (Circ J 2007; 71: 530–535)

Key Words: Calcium; Coronary artery disease; Ultrasonics

Calcification is a common finding in human coronary arteries, and has usually been interpreted as an indicator of advanced atherosclerosis! In the past few decades, arterial calcification has been considered passive and degenerative. With recent clinical and basic research, however, there is increasing recognition that arterial calcification is an active, regulated process. In particular, following the introduction of electron-beam computed tomography (EBCT), which permits the quantitative assessment of coronary artery calcification, there have been rapidly increasing numbers of clinical studies of coronary calcification. Some studies have shown that EBCT-detected coronary calcification correlates with the degree of plaque burden in the entire coronary tree. More recently, multislice computed tomography (MSCT) has allowed for the detection of not only coronary artery calcification but also coronary artery stenoses and plaques. Coronary calcifications detected by MSCT can be assessed along the long axis of the coronary artery. However, it is difficult to assess the circumference of calcium deposits using cross-sectional images obtained by MSCT.

Intravascular ultrasound (IVUS), in contrast, enables the identification of calcium deposits and exact measurements of vessel diameters and areas, including those associated with culprit lesions. A number of IVUS studies have focused on detailed assessment of calcification. However, neither total areas nor volumes of calcium deposits can be accurately determined using current IVUS technology, because calcium deposits produce acoustic shadowing. Previous studies with IVUS have demonstrated that calcification can be quantified as the arc on cross-sections. For IVUS, this approach of quantification of vessel calcium is generally accepted and acknowledged as the most reliable method of assessment of plaque calcium along the length of lesions. Another approach is to determine the length of calcium using serial cross-sectional IVUS images. However, little is known about the correlation between the largest arc and the length of each calcium deposit within the culprit lesion segment in patients with coronary artery disease. The combination of the largest arc and the length is quite complex in IVUS analysis. The question arises whether calcium deposits with larger arcs have a longer length. The present study was designed to answer this question.

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

Patients  Preinterventional IVUS images were obtained from 212
patients with acute myocardial infarction (AMI), unstable angina pectoris (UAP), or stable angina pectoris (SAP) between April 1998 and December 2001. In all patients, the procedure was performed on a native “de novo” atherosclerotic lesion considered to be the culprit lesion. We excluded patients with cardiac arrest or cardiogenic shock caused by multivessel diseases, or left main infarction and patients undergoing dialysis. Of the 212 patients in which preinterventional IVUS images were obtained, 18 were excluded from analysis because of poor image quality.

The study population thus consisted of 194 patients with AMI, UAP, or SAP. AMI was diagnosed based on a history of prolonged ischemic chest pain, characteristic ECG changes, and elevated creatine kinase (>twice the upper limit of normal range) within 24 h after the onset of pain. UAP was defined either as new onset angina within 2 months after a previous bout, or as angina with a progressive crescendo pattern, with the anginal episodes increasing in frequency and/or duration or as angina that occurred at rest, or angina occurring in the immediate postinfarct period. SAP was 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 intracoronary nitroglycerin. Studies were performed by using 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 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 the identification of the lumen. IVUS studies were recorded on super VHS videotape for offline analysis.

**Quantitative Assessment of Calcification Within the Culprit Lesion Segment**

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

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 scintigraphy stress testing. 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 CSA and plaque CSA was selected for analysis.

Calcium was defined by the presence of a bright echogenic signal with acoustic shadowing. A 10-mm-long culprit lesion segment (5 mm proximal to 5 mm distal to the culprit lesion site) was used for the assessment of calcification, in accordance with previous reports (Fig 1). In each of the 194 patients, the presence and extent of all calcium deposits within the 10-mm-long segment were quantified using serial cross-sectional IVUS images obtained every second, corresponding to images 0.5 mm apart, in accordance with previous reports. If a calcium deposit continued over the 10-mm-long segment, we followed it to the end of calcium. In each patient, the arc of each calcium deposit observed in each of the serial IVUS images was measured with a protractor centered on the lumen, and the largest arc of each calcium deposit was identified. The largest arc of calcium was classified as 1 quadrant (590°), 2 quadrants (91° to 180°), 3 quadrants (181° to 270°), or 4 quadrants (271° to 360°). In addition, in each patient, the length of each calcium deposit was calculated. Intraobserver variability in the measurement of the arc of calcium has been previously reported.

**Statistical Analysis**

Results are presented as mean ± SD. Statistical comparisons between more than 3 groups were performed by 1-way analysis of variance and post-hoc multiple comparison using Scheffe’s test. The correlation between the largest arc and the length of each calcium deposit was assessed by using simple linear regression. Furthermore, the statistical comparison of parallelism in linear regression was performed by analysis of covariance and post-hoc multiple comparison using Bonferroni’s test. Values of p<0.05 were considered significant.

**Results**

Clinical characteristics of all 194 patients are shown in Table 1. There were 73 AMI patients, 71 UAP patients, and 50 SAP patients. Table 2 shows the clinical characteristics
of patients with AMI, UAP and SAP. There were no statistically significant differences in age, sex, presence of risk factors and culprit vessel among patients with either AMI, UAP, or SAP. The 73 AMI patients had 134 calcifications, the 71 UAP patients had 85, and the 50 SAP patients had 58 calcifications. Of the calcium deposits (n=277), 204 (74%) were classified as 1 quadrant, 48 (17%) as 2 quadrant, 10 (4%) as 3 quadrant, and 15 (5%) as 4 quadrant. As shown in Fig 2, the length of calcium differed significantly among the 4 groups, and was greatest in the 4-quadrant group (1 quadrant: 2.0±1.9, 2 quadrant: 5.5±3.5, 3 quadrant: 9.2±5.0, 4 quadrant: 14.4±7.0 mm, mean±SD, p<0.0001). The mean largest arc in patients with SAP was significantly larger than that in patients with AMI or UAP (AMI: 58°±61°, UAP: 41°±46°, SAP: 120°±113°, mean±SD, p<0.0001; SAP vs AMI, p<0.0001, and SAP vs UAP, p<0.0001). Moreover, the mean length in patients with SAP was significantly longer than that in patients with AMI or UAP (AMI: 2.6±2.2, UAP: 2.2±2.9, SAP: 6.4±6.8 mm, mean±SD, p<0.0001; SAP vs AMI, p<0.0001, and SAP vs UAP, p<0.0001) (Table 2). Fig 3 shows the correla-

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**Table 2 Baseline Characteristics and Results of Calcium Measurements in Patients With AMI, UAP and SAP**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AMI (n=73)</th>
<th>UAP (n=71)</th>
<th>SAP (n=50)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>64±10</td>
<td>62±10</td>
<td>63±10</td>
<td>NS</td>
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<tr>
<td>Men, %</td>
<td>74</td>
<td>85</td>
<td>86</td>
<td>NS</td>
</tr>
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<td>Hypertension, %</td>
<td>45</td>
<td>52</td>
<td>60</td>
<td>NS</td>
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<td>Diabetes mellitus, %</td>
<td>32</td>
<td>24</td>
<td>32</td>
<td>NS</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>40</td>
<td>28</td>
<td>28</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>60</td>
<td>56</td>
<td>50</td>
<td>NS</td>
</tr>
<tr>
<td>Culprit vessel, %</td>
<td></td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>LAD</td>
<td>48</td>
<td>63</td>
<td>60</td>
<td>NS</td>
</tr>
<tr>
<td>LCx</td>
<td>14</td>
<td>6</td>
<td>8</td>
<td>NS</td>
</tr>
<tr>
<td>RCA</td>
<td>38</td>
<td>31</td>
<td>32</td>
<td>NS</td>
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</table>

**Measurements of calcium**

<table>
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<tr>
<th></th>
<th>AMI (n=73)</th>
<th>UAP (n=71)</th>
<th>SAP (n=50)</th>
</tr>
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<tr>
<td>Mean largest arc, degree</td>
<td>58±61</td>
<td>41±46</td>
<td>120±113</td>
</tr>
<tr>
<td>Mean length, mm</td>
<td>2.6±2.2</td>
<td>2.2±2.9</td>
<td>6.4±6.8</td>
</tr>
</tbody>
</table>

*NS, not significant. Other abbreviations see in Table 1. Values are mean±SD or percentages.*

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**Fig 2.** Relationship between distribution of the largest arc and the length of each calcium deposit. Statistical comparisons were performed by ANOVA and post-hoc multiple comparison, by using Scheffe’s test.

**Fig 3.** Correlation between the largest arc and length of each calcium deposit. AMI, acute myocardial infarction; UAP, unstable angina pectoris; SAP, stable angina pectoris.
Fig 4. A typical example of intravascular ultrasound images of calcium deposits with small arcs and short lengths in an acute myocardial infarction patient. Longitudinal image shows scattered calcifications within a culprit lesion segment. Cross-sectional images obtained from the culprit lesion (indicated by vertical lines in the longitudinal image) demonstrates 2 calcium deposits with small arcs. (A–C) A calcium deposit at the upper site in the longitudinal image (A; distal edge, B; middle, C; proximal edge). (D–E) A calcium deposit at the lower site in the longitudinal image (D; distal edge, E; proximal edge).

Fig 5. A typical example of intravascular ultrasound images of a calcium deposit with a large arc and a long length in a stable angina pectoris patient. The longitudinal image shows a diffuse calcification within a culprit lesion segment. Cross-sectional images obtained from the culprit lesion (indicated by vertical lines in the longitudinal image) demonstrates a calcium deposit with a large arc (A; distal edge, B and C; middle, D; proximal edge).
tion between the largest arc and the length of each calcium deposit. For the group of all patients, the length of each calcium deposit exhibited a strong correlation with the largest arc of calcium (AMI: \( R = 0.732, p < 0.0001 \), UAP: \( R = 0.576, p < 0.0001 \), SAP: \( R = 0.745, p < 0.0001 \), all patients: \( R = 0.750, p < 0.0001 \)). The slope differed significantly among the 3 groups (\( p < 0.001 \)). The slope for AMI patients was significantly smaller than that for SAP patients (\( p < 0.001 \)). Typical examples of calcium deposits with a small arc and a short length in AMI patients or with a large arc and a long length in SAP patients are shown in Figs 4 and 5.

**Discussion**

The major finding of the present study was that the length of each calcium deposit within the culprit lesion segment exhibited a positive correlation with the largest arc. Although a number of IVUS studies of calcium deposits have been performed, the approach to quantification of vessel calcium has not been standardized. Most previous studies found that calcification can be quantified by IVUS as the arc on a cross-section, using only single cross-sectional images. Scott et al reported that quantification of vessel calcium using serial cross-sectional IVUS images enables a more accurate assessment of plaque calcium along the length of the vessel. We used these approaches in the present study, and measured the arcs, lengths, and numbers of calcium deposits within the 10-mm-long culprit lesion segment, using serial cross-sectional IVUS images. By using these approaches, we showed in a recent study that significant differences existed in the pattern of coronary calcification in the culprit lesion segment, in particular with respect to size, number, and length of deposits, among patients with AMI, UAP, and SAP. Small calcium deposits were significantly more frequent in the culprit lesion segments in acute coronary syndrome (ACS) than in SAP patients. More recently, Fuji et al demonstrated that ruptured plaques are associated with a larger number of small calcium deposits. However, the correlation between the largest arc and length of calcium deposition had not been previously determined. Previous IVUS studies found that soft plaques without calcium are associated with ACS, while calcified/fibrous plaques were more common in SAP patients. Furthermore, Yamanaka et al reported that the coronary artery calcification score assessed by cinefluoroscopy in patients with ACS was significantly lower than that in those with SAP. Although it is true, as shown in the present study, that larger and longer calcifications are associated with SAP, small calcifications are common in patients with ACS. Our IVUS results do not contradict these previous findings.

Here, the important point was that the target lesion was assumed to be the culprit lesion at the time of angiography. However, the possibility cannot be excluded that acute coronary events are in fact caused by other lesions in the same vessel, especially in patients with AMI, because current IVUS technology cannot clearly distinguish between plaque and thrombus. Furthermore, changes in calcium levels along the length of the lesion must be dealt with, although neither total areas nor volumes of calcium deposits can be accurately assessed using current IVUS technology. We therefore believe that the integrated appearance of the culprit segment over a 10-mm-long segment must be considered, and that analysis of only a single cross-sectional image is insufficient.

The present study, moreover, showed that the slope of the correlation between the largest arc and the length of each calcium deposit for AMI patients was significantly smaller than that for SAP patients. Vascular calcification is a complex phenomenon, and there may be more than one mechanism of calcification in human atherosclerotic lesions. In the light of our present results, one could hypothesize that arterial calcification mechanisms and processes might be different between "unstable or ruptured" coronary plaques in AMI patients and "stable" coronary plaques in SAP patients. Further studies are needed to clarify this possibility.

Current IVUS technology has certain limitations with regard to the quantification of calcium. In the present study, we demonstrated a direct correlation between the largest arc and length of each calcium deposit within the culprit lesion segment. However, these observations do not indicate whether this approach to quantification of vessel calcium accurately represents calcium burden within the culprit lesion segment. Total calcium burden often cannot be estimated, because deeper structures that may or may not be calcified are hidden in the shadow of more superficially calcified regions. Furthermore, commonly, the length of calcium deposits was estimated by using catheter pullback techniques. Inherent errors caused by the measured pullback techniques including angulation of the catheter tip in relation of imaged calcification, catheter-induced deformation or straightening of the natural coronary tortuosity, all limit accuracy of this measure of calcium length. Despite these potential causes of errors, Kostamaa et al reported that there was an excellent correlation of the measured calcium length by histology and IVUS.

What are the clinical implications of this study? Calcium deposits were assessed along the long axis of the coronary artery by cinefluoroscopy or MSCT. Our finding, that calcium deposits of longer length can be interpreted as having a larger arc, is important to physicians performing percutaneous coronary intervention (PCI) with only information on calcium deposits detected by cinefluoroscopy or MSCT without that by IVUS, because the extent of calcium deposits influences the effectiveness of PCI. Furthermore, using non-invasive modalities, such as MSCT and magnetic resonance imaging, the natural history of coronary atherosclerosis and development of calcium deposits might be studied serially to further understand the complex relationship between calcification and plaque vulnerability. Hence, our results would provide additional information not only on the long axis of calcium deposits but also on the circumference of them.

In conclusion, the length of calcium deposits detected by IVUS within the culprit lesion segment was found to be positively correlated with the largest arc. This finding will be useful in interpreting results of previous and future IVUS studies, which deal with only the arc of calcium deposition, as well as CT studies that assess calcium deposits mainly along the long axis of the coronary artery.

**References**


