Target Lesion Calcification in Coronary Artery Disease: An Intravascular Ultrasound Study

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Objectives. The purpose of this study was to evaluate the frequency, amount and distribution of target lesion calcification in patients undergoing transcatheter therapy for symptomatic coronary artery disease.

Background. Coronary artery target lesion calcification may be an important determinant of response to transcatheter therapy: balloon angioplasty causes dissections in calcified lesions, directional atherectomy cuts calcium poorly, rotational atherectomy causes preferential ablation of calcium and laser irradiation effect may vary. Intravascular ultrasound imaging is a highly sensitive technique for detection of plaque calcification in vivo.

Methods. We performed intravascular ultrasound imaging before or after, or both, various transcatheter therapies in 110 patients. These 84 men and 26 women had a mean age of 60 years and a duration of angina of 22 ± 34 months. Forty-nine patients had one-vessel, 29 had two-vessel, 25 had three-vessel and 7 had left main coronary disease. Vessels treated and imaged were the left main (n = 7), left anterior descending (n = 47), left circumflex (n = 18) and right (n = 38) coronary arteries.

Results. Eighty-four patients (76%) had target lesion calcification; 29 patients had one-quadrant, 25 had two-quadrant, 17 had three-quadrant and 13 had four-quadrant calcification. The calcification was superficial in 42 patients, deep in 13 and both superficial and deep in 31. The axial length of calcium could be measured in 29 patients; it was ≤5 mm in 11 and ≥6 mm in 18. Fluoroscopy detected calcification in 50 patients (48%, p < 0.001 vs. detection by ultrasound); this proportion increased to 74% in patients with calcification of two or more quadrants and to 86% in patients with calcification ≥6 mm in length of two or more quadrants. Calcification was more common in patients who smoked and tended to be more common in patients with multivessel disease or previous coronary artery bypass graft surgery.

Conclusions. We conclude that target lesion calcification occurs in 75% of patients with symptomatic coronary artery disease requiring angioplasty. Target lesion calcification is best detected, localized and quantified by intravascular ultrasound. These observations may be important in selecting devices for transcatheter therapy.
patients and of previous coronary artery bypass graft surgery in 18. Thirty-eight patients were smokers; two were on maintenance dialysis.

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Patients were studied after giving written, informed consent. Intravascular ultrasound imaging is performed as part of ongoing protocols approved by the Institutional Review Board of the Washington Hospital Center.

Fluoroscopic-angiographic study. The presence of calcification in the target lesion was evaluated during fluoroscopy before the ultrasound study was performed or by persons who did not know the ultrasound results. With use of digital electronic calipers, the percent angiographic diameter stenosis was measured in orthogonal projections. The angiographic target lesion was defined as the entire length of lesion subjected to transcatheter device therapy. The mean percent angiographic diameter stenosis was 79 ± 12% (range 58% to 100%) before intervention.

Intravascular ultrasound imaging systems. We used the InterTherapy intravascular ultrasound imaging system incorporating either a 20-MHz transducer-tip catheter within a 4.9F sheath or a 25-MHz transducer-tip catheter within a 3.9F sheath. Point to point resolution along the ultrasound beam axis was calculated to be 100 μm for the 20-MHz and 80 μm for the 25-MHz catheter; the calculations are based on transducer frequency and wavelength and the speed of ultrasound transmission in tissue. The maximal penetration depth was 8 mm, which was also a function of the tissue type being imaged. Planar two-dimensional images were formed in real time by motor rotation of the entire transducer-tip catheter within the polyethylene imaging sheath at 1,800 rpm. In 40 patients, the 25-MHz tipped catheter was withdrawn within the imaging sheath at 0.5 mm/s by a prototype motorized pullback device. At this pullback rate, contiguous image slices were 17 μm apart. Studies performed in this manner provided source material for many of the illustrations in this study. Studies were recorded on high resolution 0.5-in. (1.27-cm) videotape for off-line analysis.

Three-dimensional reconstruction of the planar intravascular ultrasound images was possible in the 40 patients in whom imaging was performed with the motorized pullback mechanism. We used software developed by Pura and hardware from Image Comm. The software-encoded algorithm uses thresholding to render the three-dimensional image. The hardware can digitize 6 frames/s. Parameters were set so that 12 image slices were stacked per mm of arterial length; 230 digitized images were used to reconstruct a segment of artery 19 mm long. Regions of interest were set to include all arterial structures between the adventitia and intima and to exclude the imaging sheath. The threshold was set just low enough to exclude blood echoes. Each arterial segment either was viewed as an intact cylinder or was split in half to be viewed as two hemicylinders.

Qualitative ultrasound. Calcification is detected as bright dense echoes (brighter than the reference adventitia) with acoustic shadowing of underlying tissue. Calcification is differentiated from dense fibrous tissue by the presence of acoustic shadowing. Dense fibrous tissue also causes bright echoes (as bright as or brighter than those of the reference adventitia but usually less bright than those of calcium), but usually without acoustic shadowing (8–11). Calcification was classified as 1) superficial if it involved the lumen-intimal interface, 2) deep if it was within the plaque with ≥0.3 mm of overlying noncalcified plaque, or 3) both (Fig. 1).

Quantitative ultrasound. The circumference of atherosclerotic plaque in the target lesion occupied by calcium was measured as an arc (in °) with a protractor centered on the imaging catheter (Fig. 2). The target lesion was identified by using a fluoroscopic reference for the ultrasound catheter position to ensure accurate comparison with angiographic data. If there was more than one calcific deposit in a given imaging slice, the arcs of calcium were added. If the arcs overlapped, they were measured as a single continuous arc. 

Figure 1. Intravascular ultrasound images from six patients illustrating patterns of calcium distribution. A, C and F, Superficial calcification (solid arrows). D, Deep calcification (open arrow). B and E, Superficial (solid arrow) and deep (open arrow) calcification. In A, the adventitia shadowed by the lesion calcification is reconstructed by a dotted line; the ultrasound catheter is shown by the long white arrow.
Figure 2. Intravascular ultrasound images from four patients, illustrating the measurement of the circumferential arc of calcium. A, Noncalcified artery. B, Fibrotic-calcific atherosclerotic plaque with an arc (arrows) of calcium measuring 74° (note the shadowing of the deeper tissues beyond the calcium). C, Artery with an arc of calcium measuring 271°. D, Complete (360°) circumferential intimal calcification.

With the motorized pullback device, the length of each calcific deposit or the overall length of contiguous and overlapping calcific deposits was measured in 40 patients. With the imaging catheter moving at 0.5 mm/s, each second of recorded videotape represents a segment of artery 0.5 mm long. Two contiguous imaging slices are 17 mm apart. For the purposes of this study, the length of a calcified arterial segment was calculated from the number of seconds or the number of frames of videotape in which it appeared (Fig. 3 and 4).

With three-dimensional reconstruction, the area of intimal surface occupied by calcification could be visualized. When visualizing the artery from outside the adventitia, adventitial dropout represented underlying calcification (Fig. 5). Confirmation that adventitial dropout was caused by underlying calcification (rather than by weak acoustic penetration) was confirmed by relating the three-dimensional reconstruction to the corresponding two-dimensional image slices.

Statistical analysis. Statistical analysis was performed by using chi-square analysis, the Student t test, the Fisher exact test, analysis of variance or correlation coefficients where appropriate. Results are reported as mean value ± 1 SD.

Results

Fluoroscopic analysis. By fluoroscopy, 50 patients (48%) had calcification in the region of the target lesion treated by transcatheter therapy.

Intravascular ultrasound analysis. By intravascular ultrasound, 84 patients (76%) had target lesion calcification (p < 0.001 vs. the number detected with fluoroscopy). Forty-seven patients (56%) had a single calcific deposit; the other 37 had two or more calcific deposits. In these 84 patients the arc of calcium measured 100 ± 100° (range 0° to 360°); in 29 patients it measured ≤90°, in 25 patients 91° to 180°, in 17 patients 181° to 270° and in 13 patients 271° to 360° (Fig. 6). In 42 patients (50%) the calcification was superficial, in 13 (15%) it was deep and in 31 (35%) it was both superficial and deep.

In 40 patients the longitudinal length of single or multiple contiguous calcific deposits could be measured. Twenty-nine of these patients (73%) had target lesion calcification. The mean length was 15 ± 9 mm (range 1 to 40). In 11 patients, the length was ≤5 mm, in 6 it was 6 to 10 mm, in 7 it was 11 to 20 mm and in 5 it was >20 mm. In these 29 patients there was no significant correlation between the arcs and length of target lesion calcification (Fig. 7).

Typically, there was significant axial variability in the circumferential arc of calcification within each lesion site (Fig. 8 and 9).

Clinical correlates (Table 1). Target lesion calcium did not correlate with patient age, duration of angina or a history of hypertension, diabetes or a remote myocardial infarction. Calcification was more common in smokers (37 of 38) than in nonsmokers (49 of 72, p < 0.001) and the arc of calcium was larger in smokers than in nonsmokers (157 ± 126° vs. 83 ± 91°, p < 0.02). Calcification tended to be more common in
patients with multivessel or left main disease (53 of 61) than in patients with single-vessel disease (35 of 49, \( p = 0.060 \)) and the arc of calcification tended to be larger in the former groups (137 \( \pm 118^\circ \) vs. 81 \( \pm 79^\circ \), \( p < 0.05 \)). Similarly, target lesion calcification tended to be more common in patients with than in those without previous coronary artery bypass graft surgery (17 of 18 vs. 70 of 92, \( p = 0.076 \)) and the arc of calcification tended to be larger in this group (137 \( \pm 118^\circ \) vs. 81 \( \pm 79^\circ \), \( p < 0.05 \)). There were too few patients with insulin-dependent diabetes mellitus or chronic renal insufficiency for statistical analysis. Target lesion calcification did not correlate with the angiographic percent diameter stenosis before intervention or with lesion location or morphology.

Fluoroscopic-ultrasound correlations. Fluoroscopic target lesion calcification was more common in patients whose arc of calcification measured \( \geq 91^\circ \) (36 [74\%] of 51) than in patients whose arc measured \( < 90^\circ \) (10 [29\%] of 33, \( p < 0.001 \)).

In 40 patients, both the arc and the length of calcification could be measured. When both of these variables were considered, calcium was detected by fluoroscopy in no patient with an arc \( < 90^\circ \) and a length \( \leq 5 \) mm, 0 of 5 patients with an arc \( 91^\circ \) to \( 360^\circ \) and a length \( \geq 5 \) mm, 2 of 3 patients with an arc \( \leq 90^\circ \) and a length \( \geq 6 \) mm and 13 (86\%) of 15 of patients with an arc \( 91^\circ \) to \( 360^\circ \) and a length \( \geq 6 \) mm.

Three-dimensional reconstruction of ultrasound image slices. Intimal surface (plaque) calcification was not obviously different from a noncalcified intimal surface, and deeper tissue calcification was not seen at all. However, when viewed from outside the artery (Fig. 5), adventitial dropout accurately reflected underlying superficial and deep

Figure 4. Intravascular ultrasound images of a long, circumferential calcium deposit (arrows). Image slices shown are 5 mm apart at center; the most distal slice is at left and the most proximal slice is at right. The uninterrupted calcific deposit occupies 40 mm of axial vessel length. Extensive calcium was evident on fluoroscopic study.

Figure 5. Three-dimensional reconstruction of intravascular ultrasound images, showing the circumferential and the axial distribution of calcium. The artery is shown as two hemicylinders and is viewed from outside so that only the outermost layer (or adventitia) is seen normally. A and F show hemicylinders, 20 mm long. Adventitial dropout (short thin arrows) represents acoustic shadowing from underlying calcification. The axial length of the largest calcium deposit is from point G to point H. Panels B, C, D and E are two-dimensional image slices from this artery. The calcium in these two-dimensional image slices is shown by the open arrows. The long arrows locate these image slices within the axial length of the artery shown in F.
Lesion-associated calcification is found frequently at necropsy in patients with coronary atherosclerosis (12,13). These studies have shown that coronary artery calcification increases with the extent and severity of atherosclerosis (14), patient age (15,16) and primary or secondary chronic hypercalcemia (17). In addition, both hyperlipidemias (18,19) and chronic renal failure (20) may predispose to coronary artery calcification, the former by accelerating atherogenesis and the latter by causing chronic hypercalcemia. The highest pathologic incidence reported is 79% (4).

However, pathologic detection has limitations. Patient selection is biased and specimens usually are decalcified before staining. In vitro X-ray analysis of pathologic tissue has limited resolution and is only semiquantitative. With the motorized pullback device, it is possible to slice the artery into more and thinner slices with intravascular ultrasound than is commonly done during pathologic analyses.

High frequency intravascular ultrasound provides detailed transmural images of human coronary arteries in vivo (8–11). The normal coronary artery architecture (intima, media and adventitia) and the major components of the atherosclerotic plaque (lipid, loose and dense fibrous connective tissue, intimal hyperplasia and calcium) can be studied in vivo in a manner not possible previously.

In previous studies, the acoustic signature of arterial plaque calcium, dense fibrous tissue and soft plaque (containing lipid, loose connective tissue or intimal hyperplasia) has been validated in vitro. Using intravascular ultrasound imaging, we detected calcium in 84 (76%) of 110 lesions targeted for transcatheter therapy. This proportion approximates the highest pathologic incidence reported.

Calcification can be superficial or deep and occur in single or multiple discrete deposits. However, circumferential deposition of calcification tends to be greater than axial deposition. Short arterial segments with extensive (multi-quadrant) circumferential calcification are more common than are long segments with single-quadrant calcification.

Within any length of calcified artery, there can be extensive axial variability in the pattern of calcium deposition. Axial variability tends to be more pronounced than circumferential variability and is greater in heavily calcified than in lightly calcified arteries. Both very short calcified segments and the marked axial variability in calcium deposition are seen best with slow movement of the transducer and careful interrogation of the entire artery, which can be facilitated by motorized transducer movement. Furthermore, intravascular ultrasound imaging can differentiate target lesion calcification from calcification of contiguous arterial segments.

Many studies have used X-ray techniques to detect coronary artery calcification to screen for hemodynamically significant coronary artery disease. A meta-analysis of 13 reports (21) suggested that 58% of patients with documented coronary artery disease have fluoroscopic calcification. This frequency may be increased by using digital subtraction fluoroscopy (22), computed tomography (22–24) and ultrafast computed tomography (25,26). In our study, there was fluoroscopic calcification in 48% of lesions targeted for transcatheter therapy. With use of intravascular ultrasound imaging as the standard, fluoroscopic calcification increased with increasing amounts of target lesion calcification. Fluoroscopy detected calcium in 74% of patients with multiquadrant target lesion calcification and in 86% of patients with...
long multi-quadrant calcification and a length ≥ 6 mm. However, fluoroscopy missed all examples of short multi-quadrant calcification with a length < 5 mm.

Limitations. Our study has several limitations.

1. On pathologic study, calcific deposits have width, length and thickness. Because of acoustic shadowing artifacts, our method may minimize the true amount of calcium present. Most often, ultrasound studies were performed after transcatheter therapy, and some transcatheter therapies (for example, rotational atherectomy) remove calcium. Thus, calcification may be even more common and more extensive than our data suggest.

2. From the standpoint of impact on transcatheter therapy, the most important measurement may be the intimal surface area occupied by calcium. By measuring the intimal arc and axial length of calcium, we can approximate its surface area. Current algorithms for three-dimensional reconstruction of intravascular ultrasound images do not permit a true measurement of the intimal surface occupied by calcium. However, the surface area of adventitial dropout does reflect the surface area of underlying plaque calcification. Also, it is not possible to measure the thickness of the calcific deposits; the inner edge shadows the outer edge. Similarly, superficial plaque calcification obscures deep plaque calcification. Calcification thickness may also play an important role in arterial responses to transcatheter therapy.

Table 1. Clinical Correlates in the Study Group

<table>
<thead>
<tr>
<th></th>
<th>Calcium (no. of patients)</th>
<th>Arc of Calcium (*) (mean ± SD)</th>
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<tbody>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>37 of 38</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>49 of 72</td>
<td>157 ± 126</td>
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<tr>
<td></td>
<td></td>
<td>83 ± 91</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Yes</td>
<td>48 of 63</td>
<td>NS</td>
</tr>
<tr>
<td>No</td>
<td>39 of 47</td>
<td>95 ± 107</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100 ± 97</td>
</tr>
<tr>
<td>Remote MI</td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>30 of 38</td>
<td>NS</td>
</tr>
<tr>
<td>No</td>
<td>38 of 72</td>
<td>119 ± 105</td>
</tr>
<tr>
<td></td>
<td></td>
<td>194 ± 106</td>
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<tr>
<td>CABG</td>
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<tr>
<td>Yes</td>
<td>17 of 18</td>
<td>0.076</td>
</tr>
<tr>
<td>No</td>
<td>70 of 92</td>
<td>194 ± 106</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100 ± 98</td>
</tr>
<tr>
<td>CAD</td>
<td></td>
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<tr>
<td>1-V</td>
<td>35 of 49</td>
<td>0.060</td>
</tr>
<tr>
<td>2-V3-VLM</td>
<td>53 of 61</td>
<td>81 ± 79</td>
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<tr>
<td></td>
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<td>137 ± 118</td>
</tr>
<tr>
<td>LAD</td>
<td>36 of 47</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LCx</td>
<td>16 of 18</td>
<td>93 ± 110</td>
</tr>
<tr>
<td>RCA</td>
<td>27 of 38</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>105 ± 76</td>
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<td>86 ± 91</td>
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Values outside braces indicate p values. CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LM = left main coronary artery; MI = myocardial infarction; RCA = right coronary artery; V = vessel.
3. Few of our patients had chronic total occlusions. The plaque composition in such patients may differ from that of our study group. Plaque calcification in chronic total occlusions is important if a truly effective transcatheter therapy is to be developed, especially if this therapy is based on laser technology.

4. Our observations are limited to native vessel target lesion morphology in symptomatic patients. We did not image nontarget lesion vessels or vessels in asymptomatic patients. We have not included data on saphenous vein bypass grafts, and we also excluded patients with an acute infarction.

5. With current imaging systems, all plaque calcium looks alike. Calcium may be incorporated into atherosclerotic plaque in more than one way; the way it is incorporated may influence the structural integrity of the plaque and the arterial response to transcatheter therapy (27).

6. We did not attempt to relate procedural success to the amount or distribution of target lesion and adjacent vessel calcification. This important study needs to be done.

Implications. Calcification is a major determinant in how target lesions respond to various transcatheter therapies. Recently developed low profile imaging catheters (such as the 3.9F catheter used in 40 of our studies) makes imaging plaque in more than one way; the way it is incorporated may influence the structural integrity of the plaque and the arterial response to transcatheter therapy (27).

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References


15. Waller BP, Roberts WC. Cardiovascular disease in the very elderly. Analysis of 40 necropsy patients aged 90 years or over. Am J Cardiol 1983;51:403-21.


