Incidence, Location, Magnitude, and Clinical Correlates of Saphenous Vein Graft Calcification

An Intravascular Ultrasound and Angiographic Study

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Background—The pattern of saphenous vein graft (SVG) calcification before percutaneous intervention has not been studied.

Methods and Results—We used diagnostic and preintervention intravascular ultrasound (IVUS) to determine the incidence and magnitude of SVG calcification in 334 SVG lesions in 274 consecutive patients. Calcium was found in 133 SVGs (40%). Calcium was uniformly distributed among 48 lesion sites (14%), 43 proximal references (13%), and 42 distal references (13%). Calcium was superficial in 20 (40%) and deep in 28 (60%). Over the entire length of the SVGs, the maximum arc and length of calcium (in calcium-containing SVGs) averaged 174±107° and 6.8±4.8 mm, respectively. In calcium-containing SVGs, lesion site arc and length of calcium measured 151±107° and 4.1±3.7 mm, similar to the proximal and distal references (175±121° and 4.0±2.3 mm and 177±121° and 4.1±2.5 mm, respectively). Graft age (7.5±4.7 versus 10.5±4.7 years, P<0.0001), insulin-treated diabetes mellitus (40% versus 60%, P=0.02), and tobacco use (44% versus 55%, P=0.06) were clinical independent predictors of SVG calcification.

Conclusions—Sixty-five percent of calcium-containing SVGs had reference calcium in the absence of lesion calcium. Calcium was located primarily in SVG wall and not at the plaque. These data suggest that SVG calcium is not just part of lesion formation and maturation. SVG calcium occurred more commonly in older grafts, in insulin-treated diabetic patients, and in smokers. (Circulation. 2005;111:1148-1152.)

Key Words: grafting • calcium • ultrasonics

Previous studies have reported the frequency and clinical significance of coronary artery calcification; however, no prior study has described the frequency, pattern, distribution, and clinical correlates of calcium in saphenous vein grafts (SVGs). Therefore, the purpose of this study was (1) to use intravascular ultrasound (IVUS) to determine the arc, length, location, orientation, and distribution of SVG calcification; (2) to compare these IVUS results with angiographic findings; and (3) to correlate SVG calcification with clinical characteristics.

Methods

Demographics and Clinical Definitions

From June 1994 to September 2000, preintervention IVUS was performed in 334 lesions in 286 SVGs of 274 patients at the Washington Hospital Center, Washington, DC. This represents a consecutive series of patients with preintervention or diagnostic IVUS imaging of ≥1 diseased SVG.

An experienced research nurse obtained clinical demographics at the time of the procedure. Demographic information included gender; age; presence of hypercholesterolemia, diabetes, or hypertension; post-CABG tobacco use; family history of coronary artery disease; renal insufficiency; graft age; and de novo or SVG restenosis lesion. Diabetes mellitus was classified as insulin-dependent or non–insulin-dependent (to include oral agent or dietary glycemic control). Renal insufficiency was defined as serum creatinine ≥1.3 mg/dL.

IVUS Analysis

After administration of 200 µg of intra-SVG nitroglycerin, preintervention IVUS was performed with a commercial scanner (SCIMED/Boston Scientific) that consisted of a 30- or 40-MHz transducer mounted on the tip of a flexible shaft rotated at 1800 rpm within a 2.6F to 3.2F monorail sheath. The IVUS catheter was advanced beyond the lesion, and the automatic transducer was pulled back (at 0.5 mm/s) to the aorto-ostial junction. IVUS images were recorded onto 0.5-inch super-VHS videotape for offline analysis. Planar analysis was performed with computerized planimetry (TapeMeasure, Indec System).
Calcium was identified as very bright echoes (brighter than the adventitia) that cast acoustic shadows onto deeper tissues zones. Superficial calcium was defined as calcium located at the intima-lumen interface or closer to the lumen than to the adventitia but not deeper than the media (Figure 1). Deep calcium was located deeper than the echoluent zone that corresponded to the media (Figure 1). The orientation of the superficial or deep calcium at the lesion site was classified as concordant (center of the arc of calcium within 45° of the thickest plaque accumulation), perpendicular (center of the arc of calcium 45° to 135° relative to the thickest plaque accumulation), or opposite (center of the arc of calcium ≥135° away from the thickest plaque accumulation; Figure 2).

In addition, quantitative IVUS analysis included the following, which have been validated previously:

1. The arc of calcium was measured with a calibrated caliper (Figure 1).
2. The length was measured from the number of seconds of videotape in which calcium was identified (millimeters, equal to seconds of videotape \times 0.5 \text{ mm/s}).
3. Lesion-site external elastic membrane (EEM) and lumen cross-sectional area (CSA) at the site of the smallest lumen CSA. If >1 lesion was identified, each was analyzed independently. EEM was measured by tracing the leading edge of the hyperechoic adventitia.
4. Distal and proximal reference EEM and lumen CSA were traced similar to the lesion site. References were defined as the most normal-looking vessel within 10 mm distal and proximal to the lesion site, respectively.
5. Plaque plus media CSA was calculated as EEM minus lumen CSA.

Figure 1. Top, After tracing echoluent media circumference with computerized planimetry, SVG center was identified, and calcium arc (110°) was measured with electronic caliper. Bottom left, Superficial calcium (arrows) located at intima-lumen interface or closer to lumen than to adventitia. Bottom center and right, Deep calcium (arrows) located deeper than echo-luent zone correspondent to media.

Figure 2. Calcium orientation at lesion site (arrows). Orientation of superficial or deep calcium at lesion site was classified as concordant (center of arc of calcium within 45° of thickest plaque accumulation), perpendicular (center of arc of calcium 45° to 135° relative to thickest plaque accumulation), or opposite (center of arc of calcium ≥135° away from thickest plaque accumulation). Top, concordant; Bottom left, perpendicular; and Bottom right, opposite.
calcium was superficial in 31 (72%) and deep in 12 (28%); among 42 calcium-containing distal reference segments, calcium was superficial in 33 (78%) and deep in 9 (22%).

Among 133 calcium-containing SVGs, the average arc and length of calcium were, respectively, 151° ± 7° and 4.1 ± 3.7 mm at the lesion site, 175° ± 12° and 4.2 ± 2.3 mm at the proximal reference, and 177° ± 21° and 4.1 ± 2.5 mm at the distal reference. The maximum arc and length of calcium anywhere in these 133 SVGs were 174° ± 10° and 6.8 ± 4.8 mm, respectively.

IVUS measurements that compared SVGs with any amount of calcification versus grafts that did not have any identifiable calcium are shown in Table 2. There were no differences.

Angiographic Findings
Of the 177 angiograms that were available for analysis, calcium was detected in 29 (16%), whereas IVUS identified

6. Plaque burden was calculated as plaque plus media CSA divided by EEM CSA.

Angiographic Analysis
A core laboratory that was unaware of the ultrasound findings reviewed the angiograms. Proximal and distal anastomotic lesions were within 3 mm of the actual anastomosis. In addition to standard morphological and quantitative assessment, qualitative SVG angiographic analysis included detection of calcification (readily apparent radio-opacities within the SVG wall at the site of the lesion) and classification of calcium as none, mild (calcification barely seen on close examination), moderate (calcification readily visible before contrast injection), or severe (calcification noted without cardiac motion before contrast injection, generally compromising both sides of the vein lumen).

Statistical Analysis
Statistical analysis was performed with StatView 4.5 (SAS Institute). Categorical data are presented as frequencies and were compared with χ² statistics. Continuous variables are presented as mean ± 1SD and were compared with Student t test or ANOVA. P<0.05 was considered significant.

Results
Patient baseline characteristics are shown in Table 1.

IVUS Results
Calcium was found in 133 SVGs (40%). Calcium was equally common at the lesion site (n=48, 14%), proximal reference (n=43, 13%), and distal reference (n=42, 13%); however, graft calcification occurred more frequently within the wall (n=85, 65%) and not within the plaque (n=48, 35%).

Among the 48 calcium-containing lesions, calcium was superficial in 20 (40%) and deep in 28 (60%). Calcium was concordant to the plaque in 24 (50%), perpendicular to the plaque in 9 (18%), and opposite the plaque in 15 (32%). Among 43 calcium-containing proximal reference segments,
the presence of calcium in 73 (41%) of these 177 angiograms ($P<0.001$). In 10 SVGs (5.5%), calcium was located primarily at the lesion site; in 5 SVGs (2.8%), calcium was identified proximally; and in 14 (7.7%), calcium was diffusely distributed. Calcification was mild in 15 (8%), moderate in 7 (4%), and severe in 7 (4%). Of these, 93 lesions (52%) were concentric, whereas 84 (48%) were eccentric. Twenty-five (14%) met criteria for diffuse degeneration. Overall, reference lumen diameter measured $3.13\pm0.80 \text{ mm}$, lesion-site minimum lumen diameter measured $1.07\pm0.5 \text{ mm}$, diameter stenosis measured $68\pm14\%$, and lesion length measured $10.3\pm7.0 \text{ mm}$. There were no differences between SVGs with versus without angiographic calcium (Table 3).

**Clinical Findings**

Multivariate logistic regression analysis was used to determine independent clinical predictors of IVUS SVG calcium. Variables that were significant in the univariate analysis (Table 4) were entered into the multivariate model: gender, age, hypercholesterolemia, insulin-treated and non–insulin-treated diabetes mellitus, hypertension, history of tobacco use after CABG, family history of coronary artery disease, graft age, renal insufficiency, restenosis lesion, and proximal anastomosis. Graft age ($P<0.0001$), insulin-treated diabetes ($P=0.02$), and post-CABG tobacco use ($P=0.06$) were the only independent clinical predictors of SVG calcification.

**Findings in Native Arteries**

Thirty-one patients also had IVUS imaging of a native artery: 9 left main, 6 left anterior descending, 8 left circumflex, and 8 right coronary arteries. All 31 had calcification; lesion-site calcification was present in 30. The arc of native-artery lesion calcification measured $121\pm88\%$, with a length measuring $21\pm17 \text{ mm}$. There was no relationship between the arc and length of calcium in native arteries versus SVGs. The calcium was superficial in 61%, deep in 10%, and both superficial and deep in 29%. Native artery angiographic calcification was present in 62% (mild in 38% and moderate in 25%). There was no relationship between the presence of angiographic SVG calcium and the presence of angiographic native-artery calcium.

**Discussion**

The findings in the present study of SVG calcium are significantly different from previous IVUS reports of native-artery calcification. In the present report, only 133 (40%) of 334 SVGs contained calcium. Calcium was as common in the reference segments as at the lesion site, and calcium was more common in the vein graft wall (66%) than in the plaque (33%). In the largest previous report of native-artery lesions, 841 (73%) of 1155 target lesions contained calcium that was only superficial in 48%, only deep in 28%, and both superficial and deep in 24%. Conversely, 373 (32%) of 1155 native-artery reference segments contained calcium ($P<0.0001$ compared with target-lesion calcium). When present, reference-segment calcium was only superficial in 78%, only deep in 13%, and both superficial and deep in 9%. Only 44 native vessels (4%) had reference-segment calcium in the absence of target-lesion calcium. In the present SVG study, angiography detected calcium in only 16%, whereas in native arteries, angiography detected calcium in 38%.

Typically, veins have a thin muscle media layer and a thick adventitia layer, whereas coronary arteries have a well-developed media layer and a thinner adventitia. These anatomic features allow veins to sustain a high capacitance and a low-pressure stress and arteries to support a low capacitance and a high-pressure stress. Saphenous veins undergo “arterialization” when placed as a graft at the arterial system, with morphological changes that include intimal fibrous thickening, medial hypertrophy, and lipid deposition. Positioned in this new environment, SVGs experience a hemodynamic stress over the entire length of the conduit. In this new biological condition, SVGs should deteriorate faster than native coronary arteries. Indeed, in the present study, calcium-containing SVGs had an average arterialized age of 10.5 years, whereas native coronary arteries take many decades to exhibit any calcium. Significantly, graft calcification occurred mainly within the wall and not within the plaque, which suggests that SVG calcification is not just a result of lesion formation but also of wall changes associated with arterialization and (passive or active) degeneration. In support of this, SVG calcium was as common in the reference segments as within the lesion. Thus, we hypothesize that the pattern of calcium distribution in SVGs can be explained by hemodynamic changes caused by transferring the vein from a high-capacitance and low-pressure conduit to a low-capacitance and high-pressure conduit.

**TABLE 4. Clinical Parameters of Patients With SVGs and Any Amount of Calcium (by IVUS) Versus No Calcium (by IVUS)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>No Calcium (n=201)</th>
<th>Calcium (n=133)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>151 (45)</td>
<td>99 (30)</td>
<td>0.6</td>
</tr>
<tr>
<td>Female</td>
<td>50 (15)</td>
<td>34 (10)</td>
<td>0.6</td>
</tr>
<tr>
<td>Patient age, y</td>
<td>67.2±10</td>
<td>67.9±9.2</td>
<td>0.6</td>
</tr>
<tr>
<td>SVG age, y</td>
<td>7.5±4.7</td>
<td>10.5±4.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Insulin-treated diabetes mellitus</td>
<td>9 (40)</td>
<td>14 (60)</td>
<td>0.02</td>
</tr>
<tr>
<td>Non–insulin-treated diabetes mellitus</td>
<td>21 (60)</td>
<td>13 (40)</td>
<td>0.9</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>62 (44)</td>
<td>78 (55)</td>
<td>0.06</td>
</tr>
<tr>
<td>Hypertension</td>
<td>96 (60)</td>
<td>61 (40)</td>
<td>0.9</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>125 (60)</td>
<td>78 (40)</td>
<td>0.6</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>30 (55)</td>
<td>24 (45)</td>
<td>0.5</td>
</tr>
<tr>
<td>De novo lesion</td>
<td>107 (67)</td>
<td>64 (33)</td>
<td>0.02</td>
</tr>
<tr>
<td>Restenosis lesion</td>
<td>33 (44)</td>
<td>40 (56)</td>
<td>0.02</td>
</tr>
<tr>
<td>Distal vessel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left anterior descending artery</td>
<td>46 (50.5)</td>
<td>45 (49.5)</td>
<td>1.0</td>
</tr>
<tr>
<td>Left circumflex artery</td>
<td>69 (61)</td>
<td>44 (39)</td>
<td>0.7</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>84 (65)</td>
<td>45 (35)</td>
<td>0.1</td>
</tr>
<tr>
<td>SVG lesion location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal anastomosis</td>
<td>57 (83)</td>
<td>4 (7)</td>
<td>0.06</td>
</tr>
<tr>
<td>SVG shaft</td>
<td>219 (84)</td>
<td>40 (16)</td>
<td>0.3</td>
</tr>
<tr>
<td>Distal anastomosis</td>
<td>10 (61)</td>
<td>4 (29)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Unless otherwise indicated, values are n (%).
Calcium-containing lesions presented more frequently as restenosis compared with de novo lesions, whereas de novo SVG lesions regularly show no calcium at the lesion site, which suggests that the presence of calcium at the lesion site is a predictor of recurrent events similar to native vessels.\textsuperscript{16}

The presence of calcium deposition in native coronary arteries is a marker of future events and of the overall atherosclerotic plaque burden.\textsuperscript{16} Although most of the calcium in SVGs is located in the vessel wall (66\%) and not at the lesion, restenosis lesions had greater lesion-site calcium length (1.1±3.3 versus 0.4±1.4 mm, \(P=0.02\)), total SVG calcium length (4.6±6.1 versus 2.3±3.8 mm, \(P<0.001\)), average arc of calcium (100±122\° versus 63±104\°, \(P=0.001\)), and angiographic detection of calcium (57\% versus 20\%, \(P<0.001\)) than de novo lesions.

**Clinical Correlates and SVG Calcification**

As expected, graft age is the most important clinical marker of SVG calcification. Other markers were insulin-treated diabetes and post-CABG tobacco use. It is not clear whether insulin-treated diabetes affected the vein graft before surgery; however, we only tabulated post-CABG tobacco use, which indicates that continued smoking (not pre-CABG smoking) contributed to SVG calcification.

**Study Limitations**

The IVUS catheter was advanced beyond the lesion site but not down to the distal anastomosis in all of the procedures. Although only 177 angiograms were available for analysis, the frequency of IVUS calcium in the angiographic group was similar to that of the overall cohort.

**Conclusions**

Unlike native arteries, 65\% of SVGs that contained any calcium had reference calcium in the absence of lesion calcium, and SVG calcium was located primarily in wall and not within the plaque. This suggests that SVG calcium is not just the result of SVG lesion formation and maturation. SVG calcium occurred more commonly in older grafts, in insulin-dependent diabetic patients, and in smokers. This suggests that the hemodynamic changes associated with arterialization leads to SVG calcification.

**References**

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