Incidence and Clinical Correlates of Ruptured Plaques in Saphenous Vein Grafts
An Intravascular Ultrasound Study

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OBJECTIVES
The goal of this study was to assess the incidence, clinical correlates, and angiographic appearance of ruptured atherosclerotic plaques detected in saphenous vein grafts (SVGs).

BACKGROUND
Ruptured atherosclerotic plaques in native coronary arteries but not in SVGs have been well described with intravascular ultrasound (IVUS).

METHODS
We reviewed 791 pre-intervention IVUS SVG studies and identified 95 ruptured plaques in 76 SVGs in 73 patients. Standard clinical, angiographic, and IVUS measurements were collected and/or measured. Ruptured plaques were compared with nonruptured plaques in 276 randomly selected patients.

RESULTS
The IVUS-detected ruptured plaques had angiographically complex morphology (95%) with ulceration (79%), intimal flap (71%), and sometimes aneurysm formation (14%). Compared with control SVG lesions, ruptured plaques occurred more often in patients with acute coronary syndromes, in older SVGs (12.3 ± 5.0 years vs. 8.6 ± 5.2 years, p < 0.001), and in patients with hypercholesterolemia (92% vs. 81%, p = 0.021) and hypertension (78% vs. 63%, p = 0.015). Multiple ruptured plaques were identified in 22 patients in 19 grafts, more often in diabetic patients (55% vs. 29%, p = 0.054). A tear in the fibrous cap could be identified in 59% of plaques; in 70% it occurred at the shoulder of the plaque and in 30% at the center of the plaque. The IVUS features of ruptured plaques included positive remodeling in 71%, which was more common than in control plaques (40%, p < 0.001).

CONCLUSIONS
Ruptured atherosclerotic plaques occur in old SVGs with an incidence of 9.7%. These lesions have a complex angiographic appearance and positive remodeling characteristics. This is similar to ruptured plaques in native arteries. (J Am Coll Cardiol 2005;45:1974–9) © 2005 by the American College of Cardiology Foundation

Saphenous vein graft (SVG) disease beyond one year after coronary artery bypass grafting (CABG) is the result of rapidly progressing atherosclerosis occurring on the foundation of intimal hyperplasia (1,2). Vein graft atheromas have been shown to contain more foam cells and inflammatory cells with poorly developed or absent fibrous caps and hence are more prone to rupture (2–5). There are pathologic studies describing ruptured plaques in explanted SVGs or SVGs obtained post-mortem (6–8). Also, there is one angioscopic study reporting SVG plaque rupture (9). The features of native artery plaque rupture have been well described with use of intravascular ultrasound (IVUS) (10–13). However, there is no report on the frequency and clinical correlates of ruptured SVG plaques visualized in vivo—i.e., detected with IVUS. The goal of this study was to assess the incidence, clinical correlates, and angiographic appearance of ruptured atherosclerotic plaques detected in SVGs by use of IVUS.

*From the Cardiovascular Research Institute/Medstar Research Institute, Washington Hospital Center, Washington, DC; †Cardiovascular Research Foundation, New York, New York; and the Institute of Cardiology, Warsaw, Poland. Drs. Pregowski and Kruk were supported by the Polish Committee for Scientific Research Grant 6PO5C06121.
Manuscript received January 17, 2005; revised manuscript received February 13, 2005, accepted February 22, 2005.

METHODS
We identified 95 plaque ruptures in 76 SVGs in 73 patients. The 791 IVUS pre-interventional examinations were reviewed to collect this group. This represents the entire single-center experience with pre-intervention IVUS in SVGs. Findings in these 73 patients were compared with a randomly selected group of 276 patients with pre-intervention IVUS of an SVG lesion that did not contain plaque rupture. There was no attempt to match the two groups for clinical or IVUS characteristics.

Clinical demographics. Patient demographics were obtained by hospital chart review. Risk factors included diabetes mellitus (diet-controlled, oral medication, or insulin-treated), hypercholesterolemia (treated or >200 mg/dl), hypertension (medication-treated), and current smoking. Stable angina was defined as no change in frequency, duration, or intensity of symptoms within 6 weeks. Unstable angina was new-onset angina, accelerated angina, or rest angina. Recent myocardial infarction was defined as documented cardiac enzyme elevation greater than three times the upper limit of normal occurring within six weeks before IVUS. The date of CABG, number of venous and arterial conduits, previous myocardial infarction, percutaneous coronary intervention in other lesions, and peri-
Procedural creatine kinase-myocardial band levels were also tabulated. Peri-procedural infarction was defined as creatine kinase-myocardial band elevation from baseline normal levels to $>3$ times the upper limit of normal.

**Angiographic analyses.** Sixty percent of the angiograms were available for comparison with IVUS. The whole SVG was analyzed, not only the portion corresponding to the IVUS examination. Previously used angiographic descriptors were applied and included: *ulceration*—discrete luminal widening with luminal irregularity; *intimal flap*—radiolucent extension of the vessel wall into the arterial lumen; *lumen irregularity*—irregular lumen border not classified as ulceration; and *aneurysm*—lumen dilation $>25\%$ larger than normal segment (12) (Fig. 1). Lesions were considered complex if they had one or more of the following specific morphologies: ulceration, intimal flap, lumen irregularity, or aneurysm; otherwise, they were classified as simple. The number of complex lesions per SVG was tabulated. Plaques were considered separate complex lesions if there was an intervening fragment of SVG shaft free of any luminal irregularities. Degenerated grafts were those with lumen irregularities or ectasia comprising $>50\%$ of the length of the SVG shaft (14). Distal embolization was defined as Thrombolysis In Myocardial Infarction (TIMI) flow grade $<3$ at any stage of the procedure.

**IVUS imaging and analysis.** All IVUS studies were performed before any intervention and after intracoronary administration of $100$ to $200\ \mu g$ nitroglycerin using a commercially available system (30-MHz or 40-MHz catheters from Boston Scientific Corp./SCIMED, Minneapolis, Minnesota). The IVUS catheter was advanced distal to the lesion and pulled back at a constant speed of 0.5 mm/s to the aorto-ostial junction (automatic pullback). Qualitative and quantitative analyses were performed according to the criteria of the American College of Cardiology Clinical Expert Consensus document on IVUS (13).

Plaque ruptures were first identified by reviewing all SVG pre-interventional IVUS films (J.P. and P.T.) and required agreement of an independent experienced observer (N.J.W.). We used well-defined IVUS descriptors of ruptured plaques previously applied for native coronary artery plaque rupture. A ruptured plaque contained a cavity communicating with the lumen with an overlying residual fibrous cap fragment (Fig. 1). A fragmented and loosely adherent plaque without a distinct cavity and without a fibrous cap fragment was not considered a plaque rupture. Rupture sites separated by a length of artery containing smooth lumen contours and no cavity were considered to represent different plaque ruptures. No attempt was made to identify thrombus because it could not be distinguished from degenerated fragmented graft atheroma. Calcium deposits were brighter than the adventitia with acoustic shadowing. Hyperechoic, noncalcified plaque was as bright or brighter than the adventitia without shadowing. Hypoechoic plaque was less bright than the adventitia. When there was no dominant plaque composition, the plaque was classified as mixed.

Area measurements were performed with a commercially available program for computerized planimetry (TapeMeasure, Indec System, Mountain View, California). Cross sections with the maximal plaque cavity, minimal lumen area, maximum plaque burden (in control plaques), and proximal and distal references were identified and measured. Sites with the largest lumen and least plaque burden located within 5 mm from the rupture site were used as references. Lesion length was the distance between the proximal and distal references. The SVG area was measured by tracing the outer border of the whole vein graft with methodology previously described (15). Wall and plaque area was defined as SVG area minus lumen area. Cavity area and ruptured...
plaque lengths were measured as previously described (12). Eccentricity index was the ratio of maximum/minimum wall and plaque thickness. Eccentric plaques had an eccentricity index >3. The remodeling index was a ratio of SVG area at the lesion site and the mean SVG area at references. Positive remodeling was a remodeling index >1.

**Statistics.** Statistical analysis was performed using SPSS for Windows (SPSS Inc., Chicago, Illinois). Continuous variables were presented as mean ± 1 standard deviation and categorical variables as frequencies. Categorical variables were compared by chi-square statistics. Continuous variables were compared using the Student t test. A p value <0.05 was considered statistically significant.

**RESULTS**

**Clinical findings.** Demographic and clinical variables are shown in Table 1. Fifty-eight percent of patients also had a previous left internal thoracic artery bypass graft to the left anterior descending artery in addition to the SVGs. There were 18 patients with acute or recent myocardial infarction (MI). The duration between MI symptom onset and IVUS examination was 7.4 ± 5.9 days.

The SVG plaque rupture patients were then compared with 276 patients with pre-intervention IVUS of an SVG without plaque rupture. Ruptured plaques were found more often in older grafts, in patients with hypercholesterolemia and hypertension, and in patients with unstable coronary syndromes.

**Angiographic findings.** Angiographic findings are shown in Table 2. The locations of the ruptured plaques were distributed evenly among grafts to the left anterior descending coronary artery (24%), left circumflex artery (36%), and right coronary artery (28%); 12% were in grafts that bridged to supply more than one distal vessel. The location of the ruptured plaque was ostial in 14%, proximal one-third of the graft in 22%, middle one-third of the graft in 43%, distal one-third of the graft in 16%, and distal anastomosis in 5%. The TIMI flow grade 3 was present in all imaged SVGs before intervention, although 95% (54 of 57) of lesions were positive remodeling. Ruptured plaques, and there was a greater frequency of positive remodeling.

In 59% (56 of 95), the site of initial tear could be identified. In 70% (39 of 56), the initial tear seemed to occur at the lesion shoulder. The site with minimal lumen cross-sectional area was located within rupture site in 52% (49 of 95), distal to the rupture site in 17 plaques, and proximal to the rupture site in 29 plaques. The distance between the rupture site and the minimal lumen area site was 3.8 ± 2.9 mm. Ruptured plaques with initial tear at the shoulder tended to have a larger rupture cavity area (3.3 ± 1.9 mm² vs. 2.7 ± 1.5 mm², p = 0.14) and tended to be more often eccentric (78% vs. 59%, p = 0.17) and hypoechoic (50% vs. 26%, p = 0.075), whereas plaques that ruptured in the center more often had mixed plaque composition (67% vs. 40%, p = 0.046).

Ruptured plaques found in (angiographically) degenerated SVGs had a larger lesion SVG area (29.4 ± 13.1 mm² vs. 20.7 ± 8.5 mm², p = 0.019) and wall and plaque area (23.2 ± 15.5 mm² vs. 15.5 ± 5.8 mm², p = 0.012) and a larger mean reference SVG area (25.4 ± 10.0 mm² vs. 18.5 ± 6.8 mm², p = 0.015). However, the remodeling index was similar (1.18 ± 0.3 vs. 1.15 ± 0.2, p = 0.77).

**Table 1.** Demographics for Ruptured Plaques Versus Non-Ruptured Plaques in Control Patients

<table>
<thead>
<tr>
<th>Patients With Ruptured Plaques (n = 73)</th>
<th>Control Group (n = 276)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>68.6 ± 10.0</td>
<td>67.7 ± 9.2</td>
</tr>
<tr>
<td>Male</td>
<td>74%</td>
<td>76%</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable angina</td>
<td>28%</td>
<td>58%</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>46%</td>
<td>28%</td>
</tr>
<tr>
<td>Acute or recent myocardial infarction</td>
<td>26%</td>
<td>14%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>78%</td>
<td>63%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>36%</td>
<td>30%</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>92%</td>
<td>81%</td>
</tr>
<tr>
<td>Current smoking</td>
<td>10%</td>
<td>6%</td>
</tr>
<tr>
<td>Graft age (yrs)</td>
<td>12.3 ± 5.0</td>
<td>8.6 ± 5.2</td>
</tr>
</tbody>
</table>
Multiple plaque ruptures. There were 22 patients who had two distinct, separate ruptured plaques, including three patients with plaque ruptures in different SVGs. However, only 14 patients had imaging of two SVGs, and none had imaging of three SVGs. Patients with multiple ruptured plaques (both multiple ruptures in the same SVG and single ruptures in separate SVGs) were more often diabetic (55% vs. 29%, p = 0.054). Also, multiple ruptures were more often found in female patients (43% vs. 26%, p = 0.22).

Multiple ruptured plaques in the same SVG tended to be found more often in patients with diabetes (56% vs. 29%, p = 0.085) and hypertension (89% vs. 73%, p = 0.2). However, there was no significant relationship between female gender and presence of multiple plaques in the same SVG (37% vs. 23%, p = 0.33). The SVGs harboring multiple plaque ruptures tended to be more often degenerated (75% vs. 45%, p = 0.07) and contained more angiographically complex lesions (2.2 ± 0.8 vs. 1.7 ± 1.0, p = 0.11). However, quantitative and qualitative IVUS features of multiple versus single ruptured plaques were similar.

Comparison of ruptured versus nonruptured plaques in the same SVG. Thirty-three ruptured plaques in 25 SVGs in 24 patients were associated with 25 secondary nonruptured plaques in the same SVG. Qualitative and quantitative IVUS data are presented in Table 3. In this subset, ruptured plaque length was 3.2 ± 2.3 mm; and cavity area was 2.5 ± 1.4 mm². Calcium deposits at the lesion site were more commonly found in ruptured plaques than in nonruptured plaques.

Ruptured and control plaques had similar lesion and reference SVG area, lumen area, and wall and plaque area. However, the remodeling index was larger for ruptured than for control plaques (1.23 ± 0.25 vs. 1.07 ± 0.2, p = 0.012). Treatment. Seventy-seven ruptured plaques and 202 nonruptured plaques were stented. Angiographic distal embolization was observed in five ruptured plaque grafts in five patients. However, there were 21 peri-procedural MIs (30%) in ruptured plaques (according to the enzymatic definition) versus 29% of nonruptured plaque lesions (p = 1.0). The minimal stent area was 8.8 ± 3.5 mm² in ruptured plaques versus 8.3 ± 3.0 mm² in the control group (p = 0.5). Tissue prolapse through stent struts was observed in 12 ruptured plaque lesions, with the area of protruding tissue measuring 1.6 ± 1.1 mm² in maximum cross-sectional area and 1.8 ± 1.4 mm² in length.

**DISCUSSION**

The main findings of the current IVUS analysis are that SVG ruptured plaques: 1) occur almost exclusively in old SVGs (mean >12 years), with an incidence of 9.7% in SVGs more than 1 year of age; 2) occur in both stable and unstable patients, but more often in patients with acute coronary syndromes compared with nonruptured lesions; 3)
may be multiple; 4) almost exclusively have a complex angiographic appearance; and 5) have similar IVUS features as ruptured plaques in native coronary arteries (i.e., positive remodeling and eccentricity). It seems that plaque rupture may be a part of the natural history of vein graft disease and may correlate with graft aging, but not always with angiographically defined degeneration or lumen compromise.

Angiographic studies show that 70% to 80% of bypass surgery patients who present with acute coronary syndrome have their culprit lesion located in the SVG (2). The presence of SVG plaque rupture, a potential substrate of acute coronary syndrome in these patients, has been confirmed histopathologically (6–8). Walts et al. (6) reported ruptured plaques with superimposed thrombus in 44% of explanted SVGs resected during re-operation for graft occlusion. This is a higher incidence than in our study and may be explained by the fact that we imaged only patent SVGs and the fact that we only had 60% of angiograms available for analysis. However, similar to the current report, Walts et al. (6) reported that in some patients there may be more than one ruptured plaque in one or more SVGs and that graft age was older (between 5 and 10 years after bypass), although their group included only a few SVGs older than 10 years (8).

We found that SVG rupture plaques occur more often in patients with hypercholesterolemia. This is in line with the angiographic study by Daida et al. (16) showing that a higher preoperative cholesterol level was a strong predictor of late graft obstruction. Moreover, Solymoss et al. (17) observed that late graft thrombosis was related to an unfavorable blood lipid profile. Conversely, hypertension, found more often in patients with SVG plaque rupture in the current study, has not been shown to relate to graft occlusion or atherosclerotic graft failure in other studies (2). Our finding of a higher incidence of multiple plaque ruptures in diabetic patients corresponds with Coronary Artery Surgery Study (CASS) data showing that diabetes is a predictor of recurrent angina after bypass surgery (18). Also, the trend in the current report showing a relation between female gender and the presence of multiple SVG plaque ruptures is in keeping with CASS data showing that female patients had a higher frequency of recurrent angina after bypass surgery (18).

Using angioscopy, Silva et al. (9) reported several ulcerated SVG rupture plaques and found surface features similar to those of ulcerated plaques in native coronary arteries. However, angioscopic observations are confined to the inner surface of the vessel.

The IVUS characteristics of ruptured saphenous vein plaques included positive remodeling, the presence of calcium deposits adjacent to the plaque cavity, and eccentricity. This is similar to quantitative and qualitative IVUS descriptors of ruptured plaques in native coronary arteries—positive remodeling, a high eccentricity index, a plaque cavity that measured 2.8 mm² in area and 3.9 mm in length, a 60% frequency of shoulder-site plaque rupture, and peri-cavity calcium deposits (11–12). The similarity between SVG and native artery plaque rupture is consistent with the suggestion of Silva et al. (9) that there is a common mechanism of plaque rupture for SVGs and native arteries.

The presence of remodeling within vein grafts is controversial. Nishioka et al. (19) showed a lack of remodeling in SVGs. However, Mendelsohn et al. (20), Hong et al. (15), and Ge et al. (21) found both positive and negative remodeling in vein grafts. The fact that 70% of SVG plaque ruptures in the current study had positive remodeling (more often than nonruptured plaques in the same SVG or nonruptured plaques in SVGs in other patients) supports the presence of remodeling phenomena within SVGs and its importance to SVG disease progression.

**Study limitations.** This was a retrospective analysis. All IVUS images were recorded before any intervention, but we cannot exclude the possibility of iatrogenic plaque rupture caused by contrast injection or guidewire manipulation. The time between symptom onset and IVUS examination varied; this could have influenced lesion appearance. Medication (e.g., glycoprotein IIb/IIIa inhibitors) given to patients before the procedure varied, and we cannot exclude its impact on lesion appearance. We did not image or analyze total thrombotic occlusions. Intravascular ultrasound was not performed for the whole graft length in most cases, so the true incidence of SVG plaque rupture may be higher than we are reporting. Similarly, we only imaged SVGs that were scheduled to undergo intervention; therefore, the current observations are limited to this population. Only 60% of the angiograms were available for analysis.

**CONCLUSIONS**

Ruptured atherosclerotic plaques occur in old SVGs with an incidence of 9.7%. Patients with SVG plaque rupture have various clinical presentations, but are more often unstable with hypercholesterolemia and hypertension. As with native artery plaque ruptures, these lesions have a complex angiographic appearance and features of positive remodeling.

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