Retrieval and Analysis of Particulate Debris After Saphenous Vein Graft Intervention

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OBJECTIVES
This study was designed to evaluate the composition and quantity of particulate debris resulting from vein graft intervention.

BACKGROUND
Distal embolization and “no reflow” are frequent and important complications resulting from angioplasty of diseased saphenous vein grafts. Little is known about the composition and quantity of embolic particulate debris associated with vein graft intervention, and no intervention has been shown to protect against its clinical consequences.

METHODS
A catheter system, designed to contain, retrieve and protect against distal embolization of this material, was evaluated during 27 percutaneous interventional saphenous vein graft procedures. Clinical, angiographic and pathologic analyses were performed.

RESULTS
The duration of distal graft occlusion required to allow intervention and subsequent debris removal was 150 ± 54 s, decreasing as experience was gained. Thrombolysis in Myocardial Infarction trial (TIMI) flow grade increased from 2.6 ± 0.8 to 3.0 ± 0.0. Creatine kinase (CK) rose above normal in three patients (11.1%) exceeding 3× normal in one (3.7%) resulting in the diagnosis of non-Q-myocardial infarction. Particulate material was identified following 21 of 23 procedures suitable for analysis. Particle size was 204 ± 57 μm in the major axis and 83 ± 22 μm in the minor axis. Particles consisted predominantly of soft acellular atheromatous material, such as that typically found under a fibrous cap. Semiquantitative analysis suggested that the quantity of particulate material was less following stenting than following balloon dilation.

CONCLUSIONS
Particulate matter is commonly present following routine angioplasty and stenting of saphenous vein grafts. Containment, retrieval and analysis of this particulate debris are all feasible. Comparison to prior clinical experience is limited by small sample size. However, to the extent that these particles may contribute to distal embolization, no-reflow and infarction, such a system may contribute to the reduction of complications following vein graft intervention. (J Am Coll Cardiol 1999;34:468–75) © 1999 by the American College of Cardiology

A limitation of coronary bypass surgery has been the relatively rapid progression of atheromatous disease in aortocoronary saphenous vein grafts (1). More than one-half of such grafts have failed by 10 years, and the risk of repeat surgery is significantly greater than that of the initial procedure (2,3).

Interventional management of saphenous vein graft disease is limited by distal embolization (4,5) and “no-reflow” (6–10), which may arise from disruption of soft, friable atherosclerotic plaque and adherent thrombus (11,12). The reported incidence of distal embolization following balloon angioplasty ranges from 2% to 42%, contributing to substantial morbidity (4,6,13–17). Recognized predictors of distal embolization and infarction include the presence of diffuse disease, plaque volume, and thrombus (17). Little information is available about the composition of this particulate material, and no method has been shown to prevent distal embolization. We describe a catheter system...
designed to contain and retrieve this particulate material, the clinical and angiographic outcome following application of this system and analysis of the composition of this particulate material.

METHODS

Experimental protocol. Between July 1997 and April 1998, a total of 22 consecutive eligible patients underwent 27 vein graft angioplasty procedures utilizing a device (PercuSurge, Sunnyvale, California) designed to contain and retrieve potentially embolic particulate material. Patients were considered eligible if they were between 35 and 85 years of age with evidence of ischemia and had a >70% diameter stenosis <30 mm in length, with TIMI flow grade ≥1 in a saphenous vein graft 3.5 to 5 mm in diameter. Exclusion criteria included myocardial infarction <72 h before the procedure, uncontrolled heart failure, cardiogenic shock, coagulation disorders or a contraindication to heparin. Informed consent was obtained, and the protocol was approved by the appropriate investigational review committees.

Device description. The particulate containment and retrieval system consists of several components, as shown in Figure 1. The 210-cm angioplasty wire is constructed of 0.014 in. nitinol hypotube with a 35-mm radiopaque, shapeable, steerable tip. Incorporated in the distal wire is a 5.5-mm-long elastomeric balloon with a 0.41 to 0.43 in. crossing profile and available inflated diameters of 3.5 to 5.0 mm (Fig. 2). A detachable inflation adapter accesses the hypotube lumen by displacing a small seal, allowing inflation of the balloon. An aspiration catheter (Export, PercuSurge, Sunnyvale, California) with an internal lumen diameter of 0.040 in. allows removal of particulate debris before deflation of the occlusive balloon. The 135-cm-long aspiration catheter has a 35-cm-long distal monorail wire lumen and an external diameter of 0.072 in.

The occlusion balloon was advanced through the graft and distal to the stenosis. The inflation adapter was temporarily attached and the distal occlusion balloon inflated. Following removal of the inflation adapter, intervention was performed in a standard manner utilizing the hypotube as the angioplasty guide wire (Fig. 3). After removal of the interventional device, the aspiration catheter was advanced over the wire to the occlusion balloon. A 20-ml locking syringe was attached to the aspiration catheter to generate a vacuum and to serve as the collection chamber. Following manual aspiration, the inflation adapter was again attached.

Figure 1. Schematic of the particulate retrieval system.

Figure 2. Photograph of distal occlusion balloon and aspiration catheter.
and the distal occlusion balloon deflated, thus allowing coronary flow to resume.

**Angioplasty procedure.** Angioplasty was performed utilizing 8F guides with an internal lumen of 0.086 in. and monorail balloon catheters (Boston Scientific, Galway, Ireland). Initial patients underwent balloon predilation prior to stent deployment. Subsequent patients later underwent primary stenting without predilation. Nir (Boston Scientific, Jerusalem, Israel), biliary Palmaz-Schatz (Johnson & Johnson Interventional Systems, Warren, New Jersey), Multilink (Guidant, Temecula, California), and BeStent (Medtronic Instent, Haifa, Israel) stents measuring 9 mm to 35 mm in length were implanted. Stents were dilated utilizing the initial deployment balloon inflated to at least 12 atmospheres with a goal balloon-to-reference segment ratio of $>1.1:1$.

Patients were pretreated with aspirin 325 mg daily. Ticlopidine 500 mg daily was initiated following the procedure and continued for two weeks. Heparin was administered to achieve an activated clotting time exceeding 300 s and routinely discontinued immediately on completion. Abciximab was utilized in four patients. Dextran, dipyridamole, warfarin, thrombolytics, calcium channel blockade and nitroglycerin were not routinely utilized.

**Angiographic assessment.** Angiograms, performed in orthogonal views at baseline and after the intervention, were quantitatively analyzed at an independent core laboratory (Vancouver General Hospital). Thrombus was judged to be present if contrast angiography demonstrated an intraluminal filling defect or an abrupt vessel cutoff. “No-reflow” was defined as a new, severe reduction in coronary flow to TIMI grade 0 or 1 not due to local thrombus, spasm or dissection, implying obstruction at the level of the distal small vessels (18). Distal embolization was diagnosed when there was a filling defect, no reflow, or an abrupt cutoff in a distal coronary artery branch.

**Pathologic assessment.** Vein graft aspirate was collected in glass tubes containing EDTA-citrate buffer and transported on ice. Samples were centrifuged, the plasma removed and the pellet resuspended in incomplete Hank’s Balanced Salt Solution without calcium and magnesium. Erythrocytes were lysed with 1% saponin. The reaction was stopped by calcium gluconate, and samples were then centrifuged, resuspended and the lysis step repeated. The remaining material was fixed in 10% neutral buffered formalin or glutaraldehyde and processed for light microscopy and scanning electron microscopy.

Semiquantitative analysis was performed on 4-μm-thick paraffin-embedded sections stained with hematoxylin and eosin. Samples were considered to have maximal tissue if some atherosclerotic material was present in every high power field of the section of the precipitate, moderate if every other field showed some atherosclerotic material, and minimal when only sparse material was evident. Particle size was measured from scanning electron micrographs containing a calibrated bar. The major and minor lengths and area of each particle were determined using computer software (IP Labs, Signal Analytics, Vienna, Virginia).

**Clinical outcomes.** Total creatine kinase (CK) and creatine kinase, MB fraction (CK-MB) were measured before angioplasty, 8 h, and 16 h postangioplasty. An electrocardiogram (ECG) was obtained before angioplasty, immediately following angioplasty, if chest discomfort recurred and the following morning. Myocardial infarction was defined as an elevation of CK to $>3\times$ normal associated with elevation of CK-MB (19). Q-wave infarction was diagnosed in the presence of new Q waves in two contiguous leads. Clinical follow-up was obtained prospectively, by chart review and by telephone.

**Statistical analysis.** Results are reported as mean ± SEM. Comparisons between angiographic measurements were made with a paired $t$ tests. Group comparisons were performed by factorial ANOVA (STATVIEW 4.5, Abacus Concepts, San Francisco, California) and analyzed simultaneously with post hoc testing by the Scheffé procedure. Statistical significance was defined as $p < 0.05$.

**RESULTS**

Between July 1997 and April 1998, a total of 27 vein graft interventions were performed utilizing an emboli containment device (Table 1). Patient age was 64 ± 10 years and graft age 8.7 ± 5 years (range 2 to 12 years). Procedure time was 65 ± 25 min and fluoroscopy time 18 ± 10 min. Distal graft occlusion averaged 150 ± 54 s, decreased as experience was gained and was well tolerated. Occlusion balloon inflation volume was 1.1 ± 0.02 ml. Mean aspirate volume was 19.1 ± 5.3 ml.
Clinical outcome. All 27 procedures were technically successful, as shown in Figure 4. A total of 37 lesions were treated with implantation of 36 stents. No patient developed new Q waves, required cardiac surgery, or died. Creatine kinase remained normal (<260 U/liter) following 24 of 27 procedures and rose above normal following 3 procedures (11.1%). In one of these patients (CK 492 U/liter) a large visible thrombus was dislodged prior to distal occlusion with the GuardWire (PercuSurge Inc., Sunnyvale, California). In a second patient (CK 285 U/liter) operator error resulted in premature deflation of the occlusion balloon prior to aspiration. In a third patient (CK 1201 U/liter) with a large, bulky thrombus, no-reflow was evident despite protection, presumably due to incomplete thrombus aspiration. In this patient CK exceeded 3 times normal, resulting in the diagnosis of non-Q myocardial infarction (3.7%). At 6 ± 3 months, no patient had died, suffered late infarction or undergone cardiac surgery, whereas target lesion reintervention was undertaken in three patients.

Angiographic results. Qualitative and quantitative angiographic results are presented in Table 2. In no patient was the occlusion balloon associated with visible damage to the distal vessel. Follow-up angiography performed in nine patients at 5 ± 3 months found restenosis (stenosis >50%) in four grafts, TIMI flow grade 2.9 ± 0.4 and no evidence of new disease at the site of distal occlusion.

Pathologic assessment. A total of 49 aspirations were suitable for analysis. Particulate material was retrieved from 21 of 23 procedures. Light microscopy revealed that the particles consisted predominantly of necrotic core with cholesterol clefts, lipid-rich macrophages and fibrin material (Fig. 5). Fibrous caps and smooth muscle cells were identified, but these appeared relatively sparse. This suggested the material consisted primarily of the soft acellular atheromatous material typically found under the fibrous cap (Table 3). Scanning electron microscopy found a particle size of 204 ± 57 μm (range 8 to 3,427 μm) in the major axis and 83 ± 22 μm in the minor axis (Fig. 6).

Semiquantitative analysis of aspirates, as shown in Table 3, found both balloon angioplasty and stenting were associated with recovery of particulate debris. However, particulate material was significantly greater following balloon predilation than subsequent stenting (p = 0.43). Direct stenting without balloon predilation was associated with less particulate material than seen with balloon predilation alone and less than that associated with the combi-
nation of balloon predilation and subsequent stenting. Although suggestive, numbers were small and not statistically significant.

**DISCUSSION**

**Study findings and implications.** The principal finding of our study is that embolic atherothrombotic particulate matter is commonly liberated during angioplasty and stenting of saphenous vein grafts. This particulate matter may play a role in the pathogenesis of distal embolization, no-reflow and infarction following vein graft intervention.

**Particulate retrieval procedure.** The GuardWire system is compatible with routine angioplasty procedures and is capable of containing and then retrieving particulate debris. Event rates, including CK elevation (11.1%) and non-Q-wave myocardial infarction (3.7%), were lower than generally reported following vein graft angioplasty without such protection (17,19–21). In no case was vessel damage seen as a result of inflation of the distal occlusive balloon, and late development of a stenosis at the site of distal occlusion was not apparent.

Ischemic times required for distal occlusion and aspiration during angioplasty were well tolerated, averaging 2.5 min. Initial patients in this series underwent a staged procedure with graft aspiration and deflation of the distal occlusive balloon following predilation and stent deployment. Because these brief periods of graft occlusion were

<table>
<thead>
<tr>
<th>Samples</th>
<th>N</th>
<th>Foam Cells</th>
<th>Necrotic Core</th>
<th>Cholesterol Clefts</th>
<th>Collagen</th>
<th>Platelets</th>
<th>Overall Plaque Material</th>
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<tbody>
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<td>Balloon predilation</td>
<td>14</td>
<td>1.21 ± 0.21</td>
<td>2.21 ± 0.24</td>
<td>1.14 ± 0.31</td>
<td>0.64 ± 0.20</td>
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<td>Stenting after predilation</td>
<td>12</td>
<td>1.0 ± 0.01</td>
<td>1.67 ± 0.23</td>
<td>0.42 ± 0.19</td>
<td>0.17 ± 0.11</td>
<td>0.83 ± 0.83</td>
<td>1.15 ± 0.10*</td>
</tr>
<tr>
<td>Single-stage stenting without predilation</td>
<td>7</td>
<td>1.14 ± 0.26</td>
<td>1.57 ± 0.30</td>
<td>0.57 ± 0.30</td>
<td>0.57 ± 0.30</td>
<td>1.14 ± 0.51</td>
<td>1.27 ± 0.49</td>
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Comparison of aspirates was obtained following balloon predilation, subsequent stenting and direct stenting without balloon predilation. Semiquantitative analysis was performed on paraffin-embedded sections stained with hematoxylin and eosin. Scores were recorded as maximal (3), moderate (2), minimal (1) or absent (0) plaque material as defined in text. *Statistical differences among the three groups by repeated measures ANOVA were only observed in overall plaque material between balloon predilation versus stenting after predilation (p = 0.043). The p-value for samples comparing balloon predilation versus stenting without predilation was 0.066, and for stenting after predilation versus stenting without predilation it was 0.604.

N = cases examined.
well tolerated in early cases, a single-stage approach subsequently proved feasible and desirable.

**Stenting of vein grafts.** All patients in this series underwent stent implantation. Initial studies of the Palmaz-Schatz stent in focal vein graft stenoses reported transient no-reflow in approximately 10% of procedures (22) and a 10% to 12% incidence of non-Q-wave myocardial infarction (22–26). The Saphenous Vein De Novo Trial (27) compared the Palmaz-Schatz stent to balloon angioplasty and found a trend toward less non-Q-wave infarction (2% vs. 5%, p = 0.1). In one series, the Palmaz-Schatz biliary stent was associated with distal embolization in 23% of patients and non-Q-wave infarction in 44% (28). De Jaegere (29) reported a 11% incidence of in-hospital infarction, urgent surgery or death in a group of patients primarily treated with the Wallstent. Limited experience has been reported with the Wallstent (29–31), Wiktor (32), and Gianturco-Roubin stents (33) and covered stents (34).

**Cardiac enzymes.** Cardiac enzymes rise in 5% to 20% of patients following percutaneous coronary interventions in native vessels (19). The reported frequency of enzyme elevation following vein graft intervention is generally higher (17,19–21,34,35) in contrast to the 11.1% incidence of CK elevation and 3.7% incidence of non-Q-wave infarction (CK >3× normal) in this study. There is some debate as to a cause–effect relationship between elevations of CK, CK-MB, and adverse late clinical outcome (19).

**Comparison to alternative strategies.** Direct aspiration has been reported of angiographically visible thrombus from vein grafts utilizing standard angioplasty guiding catheters (36–38) and specially constructed thrombo-suction devices (39,40). Experience with directional atherectomy, laser and rotablator in vein grafts has been disappointing (41–45). Transluminal extractional atherectomy (InterVentional Technologies, Bellevue, Washington) may reduce cardiac enzyme release following graft intervention; however, experience has been variable, and distal embolization remains a concern (13,46–50).

Fibrinolytic drugs have been advocated as adjuncts to vein graft intervention, and local fibrinolysis has been utilized to debulk intragraft thrombus. However, reduced embolic complications have not been demonstrated (51,52). Glycoprotein IIb/IIIa inhibition may be desirable (53,54). In the EPIC trial, abciximab was associated with a reduction in distal embolization and a nonsignificant trend (14% vs. 5%) toward reduced infarction in the subgroup of patients undergoing vein graft intervention (55). However, when results of both the EPIC and EPILOG trials were combined, no benefit was found in patients undergoing vein graft intervention (53). Although secondary platelet activation by particulate matter is possible, the large amount of particulate atheroembolic material demonstrated in our study suggests a limited role for antiplatelet therapies in the prevention of distal embolization in saphenous grafts.

**Implications for stenting.** The quantity of particulate debris retrieved after balloon predilation was greater than that retrieved after subsequent stent deployment (Table 3). This supports conjecture that the screen-like configuration of stents may entrap friable material, reducing the likelihood of dislodgment and embolization (27,50). An antiembolic role for stents may have implications for optimal stent design. Greater surface coverage might be desirable for stents designed for use in vein grafts.

The quantity of particulate matter retrieved in patients who underwent balloon predilation and subsequent stenting may be greater than that retrieved in patients undergoing direct stenting without predilation. This finding suggests that balloon predilation before stenting may increase embolic debris (50) and that direct stent implantation without predilation may be desirable where possible. However, all interventions were associated with the recovery of particulate debris.

**Study limitations.** This single-center study is limited by small size, by limited angiographic follow-up, semiquantitative analysis of particulate material and the lack of a randomized control group. Comparison with prior studies must be made with caution. The possibility that some of the aspirated debris might have been removed directly from the graft wall, as opposed to the lumen, cannot be excluded,
although the direct effect of the aspiration catheter on the vein graft wall would be comparable to passage of other catheters commonly used during coronary interventions. There remains the potential risk for graft embolization during passage of the device before distal occlusion or to incomplete removal of debris. Further clinical trials will require direct comparison with routine vein graft intervention.

Finally, embolic atherothrombotic particulate matter is commonly present within saphenous vein grafts following routine angioplasty and stenting. Containment and retrieval of embolic particulate matter is feasible, and further trials of protection devices appear warranted. This particulate matter may play a role in the pathogenesis of distal embolization, no-reflow and infarction following vein graft intervention.

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