Prevention of Distal Embolization During Coronary Angioplasty in Saphenous Vein Grafts and Native Vessels Using Porous Filter Protection

Eberhard Grube, MD; Ulrich Gerckens, MD; Alan C. Yeung, MD; Sascha Rowold; Nicole Kirchhof, DVM; Jerry Sedgewick, BA; Jay S. Yadav, MD; Simon Stertzer, MD

Background—Although distal embolization and the “no-reflow” phenomenon are well described in saphenous vein graft (SVG) interventions, the frequency, magnitude, and characterization of embolized debris have not been evaluated in routine coronary interventions. A unique embolus protection device described herein provides a means of containing and retrieving plaque material dislodged during percutaneous coronary interventions. This report details the first clinical experience of the effectiveness and safety of an emboli protection system in 11 SVG lesions and 15 native coronary artery lesions.

Methods and Results—The AngioGuard Emboli Capture Guidewire (Cordis) consists of a PTCA wire with an expandable filter at the distal tip. The porous membrane permits normal distal blood flow, while trapping potential emboli by filtration. After crossing the lesion, the filter is expanded, and routine angioplasty is performed over the same wire. Emboli retrieval is achieved by collapsing the filter and retracting the emboli capture wire (ECW). In 26 patients, standard angioplasty was performed over the ECW; 20 of these 26 patients received a stent. Collected debris was sent for histopathological analysis. Plaque debris was retrieved after native coronary and SVG interventions in all cases. The ECW was positioned and retrieved without complications. No major adverse events occurred. Myocardial infarctions and no-reflow were not observed.

Conclusions—The embolization of plaque fragments frequently occurs during coronary and SVG intervention. Distal embolization leading to microvascular obstruction and no-reflow could be successfully minimized by using the ECW. (Circulation. 2001;104:2436-2441.)

Key Words: angioplasty ■ embolism ■ grafting

Percutaneous intervention for atherosclerosis has become well established for coronary and peripheral arteries and has recently been extended to the carotid vessels. Embolization has not been considered a prohibitive issue in most native coronary or peripheral intervention. However, the risk of distal embolization has been considered significant in the carotid arteries, in degenerated saphenous vein grafts (SVG), and in thrombotic lesions seen in the acute coronary syndrome.1–3 In degenerated SVGs, the risk of distal embolization is especially high, with the “no-reflow” phenomenon being reported in up to 31.8% of cases when there is evidence of thrombus and in up to 7.9% of cases with no thrombus present.4 This complication increases the risk of myocardial infarction and in-hospital death.4,5 Accordingly, a guidewire incorporating a porous filter (100-μm pores), the AngioGuard emboli capture guidewire (ECW; Cordis) was developed to prevent embolization in carotid arteries and SVGs.

This study reports the first clinical results with this ECW and establishes the frequency and magnitude of embolization in native coronary artery and SVG interventions and whether the ECW is a plausible method of preventing embolic myocardial infarction and no-reflow.

Methods

Device Description

The ECW consists of a core wire (diameter of 0.014 inches), with an integrated wire basket and a polymeric filter at the distal end of the device. The core wire is made of stainless steel. The basket consists of a thin, porous, polymeric membrane supported by a fine metal skeleton (Figure 1). The basket material is made of nickel-titanium, and the filter is made of polyurethane (pore size, 100 μm). The

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Basket diameters vary from 4.0 to 8.0 mm and fit into 3.0 to 7.5 mm coronary arteries or SVGs. The device is inserted into the body with an outer delivery sheath (2.5F) that is used to hold the filter basket in the closed position. The use of the ECW requires a guide catheter lumen diameter of 7F/0.081 inches. After crossing the lesion and reaching the distal site, the outer sheath is then pulled back, allowing basket deployment. The wire has radiopaque marking, allowing exact placement of the basket (Figure 2). During the procedure as the blood passes through the filter, emboli collect in the filter (Figure 3). Once the procedure is completed, a second outer sleeve is inserted to close the filter and remove the device.

Study Design

In 26 consecutive patients (18 men; mean age, 66 ± 2.7 years), coronary or SVG angioplasty with the support of the ECW was performed. All other aspects of the intervention (e.g., balloon angioplasty, stent deployment, or adjunctive pharmacotherapy) were performed at the operator’s discretion. All patients were treated under a protocol approved by the Institutional Ethics Committee of Freiburg, Germany. Patients were admitted to the study with acute infarction (2 patients, 7.7%), unstable coronary syndrome (11 patients, 42.3%), or stable angina (13 patients, 50%). All patients were given aspirin (100 mg/d) and clopidogrel (300 mg loading dose) before stent implantation and a bolus of 7500 IU of heparin. One patient was given tirofiban before the intervention. In 25 patients, the femoral approach was used, and in one patient, right brachial access was chosen. All patients had an ECG before and after the intervention. Serial creatine kinase (CK) and CK-MB levels (upper limit of normal value, 80 U/L for CK and 20 U/L for CK-MB) were drawn before and 6, 12 to 18, and 24 hours after the procedure. TIMI flow was assessed before device placement, before intervention with the filter basket open distal to the lesion, and after completion of the procedure, with and without the ECW in the vessel. The criteria for clinical evidence of distal embolization were occlusion of a distal branch, onset of worsened flow in a distal segment of the target vessel during the procedure, or significant postinterventional rise of CK level, which was defined as CK values more than twice the upper limit, with positive MB.

In the first 20 patients, immediately on withdrawal from the patient, the distal end of the retrieval device was placed in a test tube of 10% neutral buffered formalin and cut proximal to the basket. The test tube containing the nitinol basket, filter, and distal wire tip was sent to the pathology laboratory at the University of Minnesota for analysis.

After fixation, morphometric analysis of the size and number of particles adherent to the filter and free-floating in the fixative was performed using computerized edge detection software. Surface area calculations were performed using the 2 longest orthogonal diameters. At least 20 sections per sample were stained with hematoxylin and eosin. Sections were also stained for van Gieson, Masson’s trichrome stain, Alcian blue, phosphotungstic acid hematoxylin, and van Kossa.

Immunohistochemical staining was performed with mouse monoclonal antibodies (DAKO) to smooth muscle actin, glycoprotein Ib/IIa (CD41), and neutrophil elastase. For negative controls, the primary antibody was replaced with normal serum. Tissue sections known to express the relevant antigens served as positive controls. The stained specimens were analyzed by a single observer who was blinded to the patient’s clinical diagnosis. The specimens were analyzed for (1) the presence of extracellular matrix with single cells as part of an atherosclerotic plaque, (2) the presence of foam cells, (3) the presence of calcified deposits, (4) the presence of neutrophils, (5) the presence of artifacts, and (6) the presence of thrombus and cellular components of blood, such as platelets.
TABLE 1. Patient Demographics

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>26</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (range)</td>
<td>66±2.7 (32–80)</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>18/8</td>
</tr>
<tr>
<td>Type of angina, n (%)</td>
<td>Stable 13 (50), Unstable 11 (42)</td>
</tr>
<tr>
<td>Risk factors, n (%)</td>
<td>Arterial hypertension* 16 (62), Hyperlipidemia† 18 (69), Diabetes (on medication) 2 (7.7), Peripheral vascular disease 3 (11.5), Previous CABG surgery 11 (42), Previous PTCA 5 (19)</td>
</tr>
<tr>
<td>History of MI</td>
<td>9 (34.6)</td>
</tr>
</tbody>
</table>

* Systolic blood pressure >150 mm Hg or diastolic blood pressure >95 mm Hg. † Total cholesterol >150 mg/dL or LDL >130 mg/dL.

MI indicates myocardial infarction. Values are mean±SD or n (%).

Data Collection

Clinical report forms were completed; they noted major adverse cardiac events (death, myocardial infarction, emergent CABG) and angiographic adverse events (abrupt closure, perforation, major dissection, or no-reflow). Periprocedural myocardial infarction was defined as total CK values more than twice the upper limit with positive CK-MB. Minor complications (ie, transient ST elevation, pseudoaneurysm at puncture site) occurring during the procedure and hospitalization were also recorded. On the clinical report forms, specific emphasis was placed on the assessment of TIMI flow and postinterventional stenosis before and after the procedure and adverse events. Percent diameter stenosis was calculated by visual caliper with degenerated SVG lesions.

The technical success rate was 96.2%; in one patient (patient 6, Table 3) the ECW wire could not pass a distal stent in the right coronary artery that had a shepherd’s crook configuration. There were no major adverse events related to the device itself. Two patients developed transient ST-segment elevation. One had an occlusive dissection after stent implantation and was treated immediately with a second distal stent. No subsequent CK/CK-MB elevation or Q-waves were observed. The second patient underwent recanalization of an occluded right coronary artery with flow decrease in a side branch during the procedure, presumably due to a completely filled basket, which was placed immediately after the first successful lesion crossing after predilatation using a small balloon catheter. A large thrombus was extracted; this

Results

The patient and lesion characteristics are shown in Tables 1 and 2. The periprocedural CK/CK-MB levels are shown in Table 2, and the individual TIMI flow grade is listed in Tables 3 and 4. In the SVG group, which had a mean graft age of 8.2 years, we included ostial, midgraft, and distal lesions. The final angiographic result showed a residual stenosis of 3.2% in the native coronary arteries and 5.9% in SVGs. Two patients (patients 12 and 15 in Table 3) with evolving myocardial infarction were included in the study to evaluate the feasibility of the ECW in this clinical setting. Except for the 2 patients presenting with acute myocardial infarction, there were no significant rises in the CK levels (as defined above) or in CK-MB levels more than the upper limit of normal value, either in the native coronary patients or in those with degenerated SVG lesions.

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TABLE 2. Lesion Characteristics and CK Levels

<table>
<thead>
<tr>
<th>No. of treated lesions</th>
<th>Native Coronary Arteries</th>
<th>SVGs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion location, n</td>
<td>RCA 9</td>
<td>Ostial 2</td>
</tr>
<tr>
<td></td>
<td>LAD 4</td>
<td>Proximal third of CABG 4</td>
</tr>
<tr>
<td></td>
<td>LCx 2</td>
<td>Middle 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Distal 1</td>
</tr>
<tr>
<td>Vessel reference diameter, mm</td>
<td>3.33±0.14</td>
<td>3.56±0.19</td>
</tr>
<tr>
<td>Lesion length, mm</td>
<td>13.47±1.29</td>
<td>11.18±1.12</td>
</tr>
<tr>
<td>Thrombus-containing lesions, n</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Tortuous vessels, n</td>
<td>4</td>
<td>0</td>
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<tr>
<td>Stent placements, n</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Stenosis, %</td>
<td>Before intervention 82.5±4.1</td>
<td>89.6±2.47</td>
</tr>
<tr>
<td></td>
<td>After intervention 3.2±1.8</td>
<td>5.9±2.22</td>
</tr>
<tr>
<td>CK/CK-MB, U/L*</td>
<td>Before intervention 49±12.07/9±1.73</td>
<td>45±9.77/8.5±2.9</td>
</tr>
<tr>
<td></td>
<td>6 h after intervention 41±15.4/5.3±1.5</td>
<td>38±16.5/6.67±0.88</td>
</tr>
<tr>
<td></td>
<td>12–18 h after intervention 48±12.5/10.5±1.9</td>
<td>75±7.3/5.5±0.5</td>
</tr>
<tr>
<td></td>
<td>24 h after intervention 45±13.9/6.6±0.68</td>
<td>55±18.0/14.25±3.04</td>
</tr>
</tbody>
</table>

* Except values from the 2 patients with acute myocardial infarction.

TABLE 3. TIMI Flow in Native Coronary Arteries

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
<th>Average</th>
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<tbody>
<tr>
<td>Initial</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>3</td>
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<td>3</td>
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<td>3</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>1.93</td>
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<tr>
<td>Before PTCA with basket</td>
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<td>3</td>
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<td>3</td>
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<td>3</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>1.43</td>
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<tr>
<td>After PTCA with basket</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>...</td>
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<td>3</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>2.57</td>
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<tr>
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<td>3</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>2.67</td>
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</table>
would have caused distal embolization in an unprotected vessel. In this patient, there was a maximal CK/CK-MB of 102/18 U/L at follow-up. Debris was retrieved from all patients, and in 24 of the 26, it was grossly visible (Figure 4).

Native Coronary Arteries
The initial flow in 10 of 13 patients with elective PTCA was TIMI 2 to 3 (Table 3); in 3 patients (patients 1, 3, and 5 in Table 3), the initial distal flow was severely reduced (TIMI 1). Normal distal run-off was observed in all patients with the ECW open distal to the lesion. None of these patients developed no-reflow. In those patients with acute myocardial infarction, after recanalization of the target vessel and PTCA of the culprit lesion, an adequate TIMI flow (TIMI II) was finally achieved (Table 3). These patients developed a maximum CK level of up to 1151 U/L (CK-MB, 158 U/L), with an early peak at 6 hours after the intervention, indicating washout phenomenon after infarct artery recanalization. The CK values of these 2 patients were excluded in the averaged CK levels (Table 2). These occluded, infarct-related arteries were crossed easily with the ECW.

Saphenous Vein Grafts
The TIMI flow before, during, and after intervention in the patient cohort with SVGs is shown in Table 4 and Figure 5. Distal blood flow in the SVGs was unchanged after the placement and opening of the porous basket, but 4 of 11 patients exhibited flow decrement after balloon angioplasty and stent placement (2 patients with flow decrease from grade 3 to 2 and 2 patients with TIMI 0). However, after collapsing and extracting the basket, normal blood flow was immediately re-established. Neither of these patients experienced an increase in CK/CK-MB. This phenomenon was only observed in large grafts with complex lesions, indicating significant obstruction of the filter pores with liberated debris. There was no evidence of distal embolization after the procedure in this high-risk patient group. Two patients developed a pseudoaneurysm at the right femoral artery, one of which required subsequent surgery. Neither of these adverse events was related to the use of the device.

Morphometric and Histological Analysis
The devices used in the initial 20 patients (15 coronary, 5 SVG) were sent for morphometric and histological analysis. Deposits covered from 5% to 80% of the filter surface area (mean, 38±26%). Particles were recovered from all devices, and the number of particles ranged from 20 to 361, with the mean being 147±111. Mean particle size was 0.10±0.5 mm², with a range of 0.015 to 20 mm². The larger “particles” were aggregates of smaller particles that seemed to have been compressed together in the filter basket and capture sheath. The mean embolic burden per patient was 37±36 mm², with a range of 0.6 to 110 mm². There was a positive correlation between lesion severity and total embolic load (r²=0.59), but it was not statistically significant. The mean embolic load retrieved from vein grafts was 35.4±30 mm²; from coronary arteries, it was 29.7±37 mm². Because all but 3 of the patients received stents, meaningful comparisons between the stented and nonstented groups were not possible.

Histologically, the vast majority of particles retrieved from the fixative solution or adherent to the filter or capture sheath were characterized by the presence of abundant amorphous extracellular matrix, with only a few cells. This hypocellular

<table>
<thead>
<tr>
<th>TABLE 4. TIMI Flow in SVGs</th>
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<tbody>
<tr>
<td>Patient</td>
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<tr>
<td>---------------------------</td>
</tr>
<tr>
<td>Initial</td>
</tr>
<tr>
<td>Before PTCA with basket</td>
</tr>
<tr>
<td>After PTCA with basket</td>
</tr>
<tr>
<td>Final</td>
</tr>
</tbody>
</table>
matrix stained positive with Alcian blue, stained strongly for von Willebrand factor, and was negative for CD41, which led to classification as chronic thrombus and atheromatous components. Neutrophils were found in almost all cases; lymphocytes and macrophages were much less common. Foam cells were often seen, but cholesterol clefts and calcified deposits were less common. Occasionally, collagen fibers and smooth muscle cells were present. An intact endothelial cell layer associated with the underlying plaque component was present in one case. Staining for glycoprotein IIb/IIIa was always negative. Acute thrombus and aggregated platelets were very rare.

**Discussion**

Embolization has not been considered a frequent event in coronary intervention. Only in the subgroup of patients with degenerated SVGs has embolization been thought to be clinically important. This study provides the first direct evidence that embolization of arterial plaque components occurs routinely during native coronary artery intervention in both right and left coronary arteries and in vein grafts.

A number of recent clinical and imaging trials have provided circumstantial evidence that microvascular obstruction, presumably due to embolization, is associated with adverse clinical outcomes. In acute myocardial infarction, Ito and colleagues showed >25% of patients with TIMI-3 flow had perfusion defects by myocardial contrast echocardiography. MRI perfusion studies have confirmed this finding and demonstrated worsening of clinical outcomes in patients with microvascular obstruction after reperfusion therapy for myocardial infarction. The surprising finding of a decrease in TIMI-3 flow in patients with acute myocardial infarction who were treated with stenting compared with angioplasty would be explainable on the basis of increased embolization with the more aggressive intervention techniques.

Along with the aggressiveness of the revascularization technique, diffuseness of atherosclerotic disease is a major predictor of adverse outcomes. Mehran and colleagues recently quantified plaque burden using intravascular ultrasound during coronary intervention and correlated it with major adverse cardiac events. The lesion plaque volume was the strongest independent predictor of adverse clinical outcomes. Increased plaque embolization due to larger plaque burdens provides the most cogent explanation for these findings.

Embolization is the major cause of acute complications during SVG intervention. During angioplasty in SVGs, Lefkovits et al reported a 10-fold increase in the risk of an adverse acute outcome (death, myocardial infarction, repeat CABG) associated with distal embolization. Within a decade after surgery, half of all bypass SVGs have severe atherosclerotic disease, and within 5 years, ~20% are reported to be occluded. Repeat bypass operation is associated with a significant risk for the patient, leaving percutaneous angioplasty as the best alternative for many patients. As a result, new devices have been developed to limit distal embolization; these include the intracoronary administration of urokinase, extraction coronary athrectomy, directional coronary athrectomy, laser angioplasty, ultrasound thrombolysis, and AngioJet rapid thrombectomy. Unfortunately, these techniques have generally failed to reduce distal embolization adequately.

We and others recently published the first results using a balloon occlusion distal embolization protection device in SVGs that was effective in preventing embolization but did not allow angiography or perfusion during the procedure. The ECW, however, ensures normal blood flow at all times during the procedure. This allows unrestricted angiographic guidance for angioplasty and stent placement. Nevertheless, voluminous debris collected within the filter can temporarily occlude distal flow, as shown in 4 patients in this study. To differentiate between flow obstruction by dissection and flow obstruction by debris collected in the basket, it is helpful to insert the capture sheath partially and re-establish distal flow by partially collapsing the basket. In contradistinction to coronary intervention, glycoprotein IIb/IIIa antagonists do not reduce the incidence of acute events in these patients, suggesting that large embolic burdens can overwhelm effective platelet inhibition.

The subjects in the present study had a wide range of embolic burdens. There was a trend toward correlation with lesion plaque volume and stenting, but the small sample size rendered these findings nonsignificant. SVGs had substantially larger embolic loads compared with native coronary arteries, but the histological constituents were similar between the 2 groups.

For the initial experience using this new distal protection device, we did not attempt to establish its superiority to conventional procedures. Retrospectively, comparison of the CK levels and TIMI flow of this heterogeneous patient population with those of patients undergoing percutaneous interventions using conventional techniques can be misleading. Certainly from the control arms of the glycoprotein IIb/IIIa inhibitor trials, the incidence of myocardial infarction, as defined by a rise in CK, can be in the range of 10% in native vessel interventions and up to 18% in vein graft interventions. The goal of our study is to demonstrate that embolization occurs very frequently during routine coronary intervention and may provide a theoretical framework for explaining some of the adverse results shown in a large body of clinical trials and observations. Therefore, further randomized trials are required to evaluate the clinical impact of distal protection devices during percutaneous coronary interventions.

**References**


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