Distal Protection With a Filter Device During Coronary Stenting in Patients With Stable and Unstable Angina

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***Background*—**Filter protection after percutaneous coronary intervention (PCI) is now available to prevent distal embolization. The aims of this study were (1) to evaluate the microembolization phenomenon during procedures of stent implantation in native coronary arteries of patients with stable and unstable angina, (2) to assess the amount and characteristics of the debris captured by the Angioguard, and (3) to investigate the relation between clinical and angiographic variables and pathological data.

***Methods and Results*—**Elective coronary stenting with the use of a protective filter was attempted in 39 consecutive coronary artery lesions with >60% stenosis (mean, 67.6±8.79%). Debris was present in 75.6% of the filters. Particle size ranged from 47.16 to 2503.48 μm (mean, 518.83±319.61 μm) in the major axis. Particles >300 μm were found in 24 of 28 filters with debris (85.7%), and particles >1000 μm were present in 10 of 28 filters (35.7%). Patients with unstable angina had greater particles (mean maximum longitudinal diameter, 1098.33±714.3 μm) than those with stable angina (412.91±453 μm; $P<0.001$). The presence of unstable angina (OR, 65; CI, 1.2 to 3420; $P=0.03$) and age >67 years (OR, 42; CI, 1 to 1698; $P=0.04$) were found to be the only independent predictors of embolic particle size.

***Conclusions*—**By limiting embolization, protective devices may prevent a number of potentially unfavorable events, thereby improving outcome. Our data support the use of these devices, especially in lesions with higher embolic potential, such as those occurring in older patients and in those with unstable angina. **(*Circulation*. 2004;110:515-521.)**

Key Words: angioplasty ■ stents ■ embolism ■ pathology ■ coronary disease

Percutaneous dilatation of coronary stenosis invariably causes plaque disruption, which may lead to distal embolization of plaque debris or thrombus material. Until recently, however, distal embolization after percutaneous coronary intervention (PCI) has been considered clinically relevant in degenerated saphenous vein grafts[1] but rather uncommon in native coronary arteries. However, several recent studies have shown that biochemical markers of myocardial injury rise significantly in a substantial proportion of patients undergoing PCI.[2–6] Biochemical signs of myocardial necrosis occur more frequently after procedures that cause a greater injury to the vessel wall, such as atherectomy or stenting, and are less common after balloon angioplasty.[2,6] Also, elevation of cardiac enzymes often occurs in otherwise successful procedures, in the absence of prolonged occlusion or reduction of flow in the target vessel or in side branches. Therefore, distal microembolization has been considered the most likely cause of increases in the markers of myocardial injury.[7] Clinical, laboratory, and histological evidence indicates that embolization often occurs and may imply an adverse prognosis.[3–6] Nevertheless, little attention has thus far been given to the detection and prevention of this event in native coronary arteries.

Recently, a few protective devices able to prevent particulate debris from embolizing distally after PCI have been developed.[8–11] Among others, the Angioguard device (Cordis Corp) is a guidewire equipped with a filter basket at the distal end designed to trap emboli during intravascular interventions.

The aim of this study was threefold: (1) to evaluate the microembolization phenomenon during procedures of stent implantation in native coronary arteries of patients with stable and unstable angina, (2) to assess the amount and characteristics of the debris captured by the Angioguard, and (3) to investigate the relation between clinical and angiographic variables and pathological data.

Methods

Study Design

This single-center, prospective study was approved by the Ethical Committee of our institution, and a written informed consent was obtained from all the enrolled patients.

Patients undergoing stent implantation for a de novo lesion of a native coronary artery were considered for the study. Clinical exclusion criteria were acute myocardial infarction within 7 days or chest pain at rest within 48 hours (unstable angina class III according

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to the Braunwald classification[12]). Angiographic exclusion criteria included distal lesion location, vessel diameter <3.0 mm by online quantitative coronary angiography, tortuosity, diffuse disease or angiographic evidence of thrombus in the target vessel, presence of a side branch ≥2.0 mm in diameter at the site of the lesion, tapering or branching of the vessel distal to the target lesion preventing the correct placement of the filter, and total vessel occlusion with Thrombolysis in Myocardial Infarction (TIMI) flow grade 0 or 1.[13]

The Angioguard device is a single-use, steerable 0.014-in guidewire equipped with a filter basket at the distal end. During the procedure, plaque debris is collected by the filter, whereas the blood can flow freely through the porous membrane. At the end of the procedure, the filter basket retaining the embolic material is collapsed again by use of another sheath and removed through the guiding catheter.

Procedure

All patients received aspirin 100 mg/d and ticlopidine 500 mg before the procedure. The use of glycoprotein IIb/IIIa inhibitors was left to the operator's judgment. Unfractionated heparin was administered to maintain an activated clotting time between 250 and 300 seconds. The procedure was performed by the femoral approach using a 7F guiding catheter. Serum creatine kinase MB fraction (CK-MB) was assessed 8 and 24 hours after the procedure.

Qualitative and quantitative angiographic parameters of the treated vessel were evaluated before and after the procedure.[14,15]

Moreover, plaque area recognized as an index of plaque burden was calculated by the quantitative coronary angiography software.

Pathological Evaluation

The tip of the Angioguard device was cut and processed for macroscopic morphometric analysis (Image-Pro plus computer software by Media Cybernetics) and light microscopy.[16]

The following quantitative parameters were assessed: (1) the percentage of the area of the filter membrane occupied by debris, (2) the number of the captured particles, (3) the 2 longest perpendicular diameters of the largest particles (particle size), and (4) the embolic burden obtained by summarizing the surface area of each particle for every patients. These parameters were assumed to represent quantitative indexes of embolization. Finally, the material was gently removed from the filter and processed for histology. Paraffin-embedded serial sections 5 μm thick were stained with hematoxylin and eosin, azan Mallory modified by Heidenhaim trichrome, and Masson's trichrome. The specimens were analyzed by 2 expert pathologists who were blinded to the patient's clinical diagnosis. The specimens were analyzed for the presence of thrombus material (fibrin, platelets, and red and white cells) and for the presence of atherosclerotic plaque tissue (extracellular matrix, necrotic gruel, fibrous fragments, foam cells, cholesterol clefts, and calcium deposits).

Definitions and Statistical Analysis

Device success was defined as successful deployment and retrieval of the Angioguard device without angiographic complications, such as dissection, spasm, or thrombosis. Myocardial infarction was defined as an increase in CK-MB exceeding 3 times the upper normal value.

Continuous variables are presented as mean±SD, and discrete variables are reported as counts and percentages. The differences between groups were assessed with a Fisher's exact test for categorical variables. A Mann-Whitney *U* test was performed to compare independent variables of 2 nonhomogeneous groups. The relation between quantitative angiographic parameters and quantitative indexes of embolization was assessed by use of linear regression analysis.

A multiple logistic regression analysis was used to investigate the predictive value of baseline and procedural variables on the quantitative indexes of embolization. The variables included in the model were age, sex, cardiovascular risk factors, previous myocardial infarction, previous surgical or percutaneous coronary revascularization, unstable angina, target vessel, direct stenting, quantitative angiographic parameters, stent implantation pressure, and postprocedural CK-MB elevation. Continuous variables were dichotomized at their median value. Results were expressed with ORs and their associated 95% CIs.

All statistical analyses were performed with the SPSS statistical software package (SPSS Inc). A probability value of $P<0.05$ was considered statistically significant.

TABLE 1. Baseline Patient Characteristics (n=35)

Characteristics	Values
Male sex	25 (71.4)
Age, y	66.3±8.73
Family history	10 (28.6)
Dyslipidemia	15 (42.9)
Hypertension	20 (57.1)
Diabetes	9 (25.7)
Current smoker	12 (34.3)
Previous smoker	12 (34.3)
Previous CABG	4 (11.4)
Previous myocardial infarction	15 (42.9)
Angina	
Stable	19 (54.3)
Unstable	16 (45.7)
No. of diseased vessels	
One	17 (48.6)
Two	15 (42.9)
Three	3 (8.6)
Left ventricular ejection fraction	60.8±11.7
Pre-PCI IIb/IIIa inhibitors	8 (22.9)

Values are n (%) except as noted. CABG indicates coronary artery bypass graft surgery; PCI, percutaneous coronary intervention.

Results

Procedural Results

Positioning of the Angioguard device was attempted in 39 lesions with >60% stenosis (mean 67.6±8.79%) in 36 patients, and device success was attained in 37 lesions (94.9%) in 35 patients. In the remaining 2 lesions, the device could not be advanced across the stenosis. These 2 lesions were managed successfully with the conventional technique and were excluded from further analysis. In all lesions, the procedure resulted in a residual stenosis of <30%. In 2 procedures, blood flow decreased after stent implantation while the filter was in place but returned to normal after device withdrawal. In no case was an alteration of the arterial wall at the site of the filter deployment detected at angiography. Postprocedural CK-MB values in patients with device success were normal in 30 patients and elevated in 5. However, in only 1 patient did the postprocedural CK-MB exceed 3 times the upper normal value. This was the only adverse event observed during hospitalization. The patients' baseline characteristics are shown in Table 1, and lesion and procedural variables are shown in Table 2.

Histopathological Results

The results of histopathological analysis are shown in Table 3. Particles could be detected in 28 of 37 filters (75.6%), with a mean particle number of 10.8±6.03 (Figures 1 and 2). The average covered area of the plastic filter was 26.3±20.17%. Particle size ranged from 47.16 to 2503.48 μm (mean, 518.83±319.61 μm) in the major axis and from 27.95 to 1214.61 μm (mean, 242.5±122.46 μm) in the minor axis. The distribution of particle size is shown in Figure 3, which shows that 50% of the retrieved particles had a diameter >600 μm. The mean embolic burden per patient, assessed as mean surface area of all the particles for each patient, was 2. 41±1.8 mm^2, with a range of 0.25 to 6.78 mm^2.

Risk Factors for Embolization on Univariate Analysis

No significant correlation between quantitative angiographic parameters and quantitative indexes of embolization was identified. In particular, this was true for plaque area, which can be considered an angiographic index of plaque burden (Figure 4).

The captured particles were statistically significantly larger in patients with unstable angina than in those with stable angina (1098.33±714.30 versus 412.91±453 μm, *P*=0.001) and were larger in eccentric plaques than in concentric ones (1096.59±610.23 versus 605.18±659.79 μm, *P*=0.03) (Table 4). No other significant association between baseline and procedural variables, the pressure of stent implantation, postprocedural CK-MB elevation, and particle size was identified. Moreover, no univariate predictor of the other quantitative indexes of embolization (percentage of filter area occupied by debris, number of particles, and embolic burden) was found.

Risk Factors for Embolization on Multivariate Analysis

The presence of unstable angina (OR, 65; CI, 1.2 to 3420; *P*=0.03) and age >67 years (OR, 42; CI, 1 to 1698; *P*=0.04) were the only independent predictors of embolization of particles larger than 600 μm. Furthermore, no variable was found to be independently associated with the percentage filter area occupied by debris, with the number of particles, or with the embolic burden.

Qualitative Evaluation

Qualitative analysis, performed with light microscopy, confirmed that the particles were characterized by fibrin strand–entrapped platelets, leukocytes, and red cells suggestive of thrombus material, fibrous tissue, calcium spots, soft acellular and amorphous material, macrophages, foam cells, and more rarely cholesterol clefts, typically identifiable in atheromatous plaques (Figure 5). The assessment made on the retrieved material revealed that thrombotic components accounted for 74.3±13.1% of the debris, whereas plaque fragments accounted for 25.7±13.1%. The retrieved material was not qualitatively different in patients with stable and unstable angina. In patients with stable angina, the thrombotic component was 69.6±7.2%, whereas in those with unstable angina, it was 78.9±16% (*P*=NS) (Table 5). No association between baseline or procedural variables and qualitative data of the retrieved material was found.

TABLE 2. Baseline Lesion Characteristics, Procedural Variables, and Quantitative Angiographic Data (n=37)

Characteristic	Value
Treated vessel	
LAD	12 (32.4%)
RCA	18 (48.6%)
LCx	7 (18.9%)
AHA/ACC type	
A/B1	25 (67.6%)
B2/C	12 (32.4%)
Eccentricity	30 (81.1%)
Irregular borders	4 (10.8%)
Calcified	5 (13.5%)
Direct stenting	28 (75.7%)
Stent diameter, mm	3.47±0.39
Stent length, mm	16.0±4.28
Maximal pressure, atm	18.9±3.42
Reference diameter, mm	3.11±0.48
Preprocedural minimal luminal diameter, mm	1.04±0.33
Preprocedural % stenosis	67.36±8.95
Preprocedural lesion length, mm	13.3±7.08
Preprocedural plaque area, mm^2	15.26±7.72
Postprocedural minimal luminal diameter, mm	3.07±0.39
Postprocedural % stenosis	7.1±8.94

LAD indicates left anterior descending coronary artery; LCx, left circumflex artery; RCA, right coronary artery; and AHA/ACC, American Heart Association/American College of Cardiology. Values are n (%) except as noted.

TABLE 3. Pathological Data on 37 Filters

Parameter	Value
Macroscopic presence of debris	25 (67.5%)
Presence of particulate material at microscopic evaluation	28 (75.6%)
Covered area on filter, %	26.3±20.17
Embolic burden, mm^2	2.41±1.8
In stable angina	2.36±1.9
In unstable angina	2.47±1.8
Particle size, mm	
Major axis	518.83±319.61
Range	47.16 to 2503.48
Minor axis	242.5±122.46
range	27.95 to 1214.61
No. of particles per filter	10.8±6.03
Filters with particles >300 μm major axis	24 (64.9%)
Filters with particles >600 μm major axis	18 (48.6%)
Filters with particles >1000 μm major axis	10 (27.0%)

Values are n (%) except as noted.

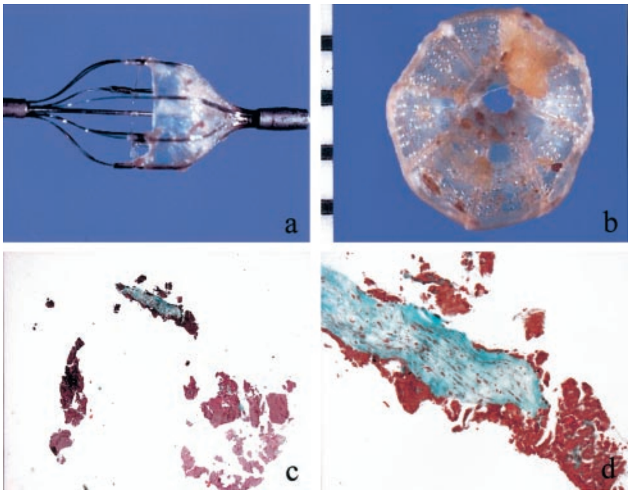

Figure 1. Filter protection device retrieved after procedure: outside (a) and inside (b) views showing embolic material from a patient with unstable angina. Histology, at lower (c) and higher (d) magnification, shows fibrocellular fragments and fragments with fibrin-platelet thrombus. Masson's trichrome stain; original magnification, ×6 (c) and ×31 (d).

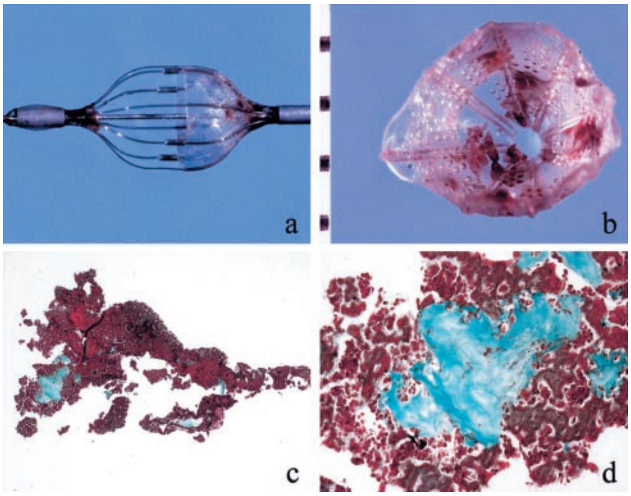

Figure 2. Filter protection device retrieved after procedure: outside (a) and inside (b) views showing embolic material from a patient with stable angina. Histology, at lower (c) and higher (d) magnification, shows a thrombus entrapping a fibrous fragment. Masson's trichrome stain; original magnification, ×4 (c) and ×20 (d).

Discussion

Our study shows that embolization of a significant amount of plaque fragments is a common event after stent implantation in native coronary arteries of patients with both stable and unstable angina. In fact, particles could be detected in 75% of the filters, with a mean particle size of 581.8 μm. Moreover, particles >300 μm were found in 24 filters (64.9%), and fragments of >1000 μm were seen in 10 (27.0%). Analysis of particle size distribution revealed that >60% of the fragments could produce arterial obstruction even before reaching the microcirculation.

Factors Associated With Embolization

The lack of association between pathological morphometric evaluation and angiographic indexes of plaque burden suggests that plaque composition can be more important in determining embolization than the plaque size.

The association between plaque composition and embolization was also suggested by the results of multivariate analysis, which showed that unstable lesions and lesions of older patients released embolic material with larger particles. This finding is consistent with the observation that coronary stenting in unstable angina is associated with a greater incidence and magnitude of myocardial injury.[5]

The univariate finding that eccentric lesions produced larger emboli also suggests that plaque composition may determine the size of embolizing fragments.

Previous studies consistently demonstrated that eccentric and angiographically complex stenoses are markers of histologically "complicated" and more unstable plaque substrates.[17–21] In atherectomy specimens of patients with stable and unstable angina, thrombus and plaque disruption were present in 57% and 81% of angiographically complex lesions, respectively.[22] In patients with unstable angina, complex angiographic lesion morphology was associated with a higher Braunwald class and worse prognosis.[23,24]

The number of embolizing particles and the percent filter area occupied by debris were not predicted by any of

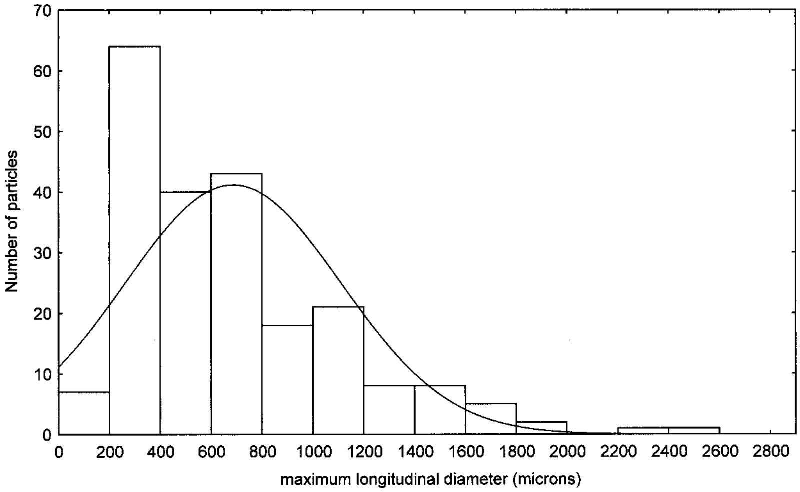

Figure 3. Distribution of particle size captured during coronary artery stenting according to maximum longitudinal diameter.

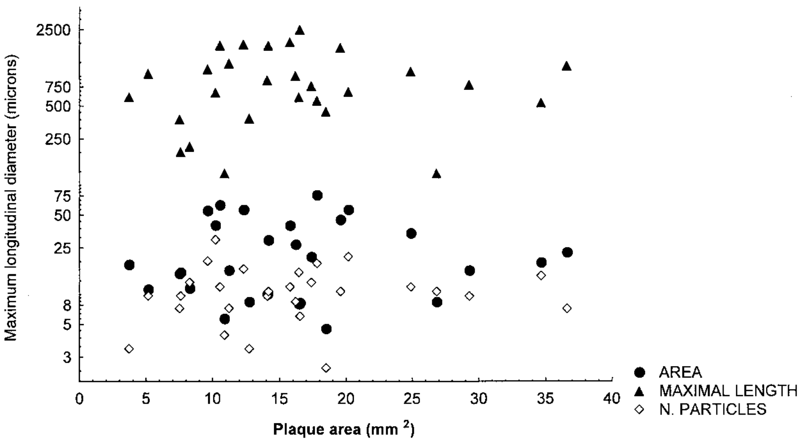

Figure 4. Scatterplots demonstrating absence of correlation between angiographic plaque area and quantitative indexes of embolization (size and number of particles and percent filter area occupied by debris).

the variables tested. However, the size of the embolic fragments may be considered the most relevant of the quantitative indexes of embolization evaluated in the study, because larger emboli can cause greater damage by obstructing larger arteries.

The lack of association between baseline or angiographic or procedural variables and quality of the retrieved material is in keeping with the evidence that histopathological features of atherosclerotic plaques are not pathognomonic of any clinical acute coronary syndromes. Although the thrombotic component was slightly higher in the unstable angina patients, the difference between stable and unstable angina patients was not statistically significant. This could be because of the exclusion criteria of angiographic evidence of thrombus in the target vessel.

Relevance of the Study

Distal protection using either occlusion balloons or filtering devices has been shown to be effective in preventing embolization of atheromatous material dislodged during vascular interventions in carotid arteries[8,16,25] and in saphenous vein grafts.[9,10,26] However, very few data are available on the use of protective devices in native coronary arteries.[10,27,28] In fact, our study, apart from being the result of the first systematic application of such an approach in native coronary arteries, is the first that addresses the relation between qualitative and quantitative characteristics of the material captured by the filter and the baseline clinical, angiographic, and procedural variables.

TABLE 4. Maximum Diameter of the Particles According to Selected Baseline and Procedural Variables

	Maximum Diameter of Particle, μm		
Type of Variable	Variable Present	Variable Absent	*P*
Age >67 y	885.31±686.83	965.52±522.1	NS
Diabetes	670.42±419.85	991.32±657.05	NS
Hypertension	947.87±679.88	888.81±562.09	NS
Dyslipidemia	835.31±534.78	998.18±697.76	NS
Family history	1119.82±750.31	829.12±548.37	NS
Smoking	946.24±535.9	872.55±808.55	NS
Unstable angina	1098.33±714.30	412.91±453.00	0.007
Eccentric plaque	1096.59±610.23	605.18±659.79	0.03
Calcific plaque	662.84±443.75	953.72±639.41	NS
Direct stenting	894.14±675.55	982.55±520.56	NS

Clinical Implications

Distal microembolization of the coronary circulation has been considered the most frequent cause of periprocedural increases of biochemical markers of myocardial necrosis.[11] This event, even when occurring in otherwise successful procedures, is associated with an unfavorable long-term outcome.[11] The role of embolizing debris in causing microvascular obstruction during coronary interventions is clearly shown by our study as well as by a previous investigation.[10] Indeed, the size of most of the emboli trapped by the filter is far too large to cross the microvascular bed.

Another in vivo demonstration of the role of microembolization of plaque fragments was provided by the study by Kotani et al,[7] who showed that in patients with acute

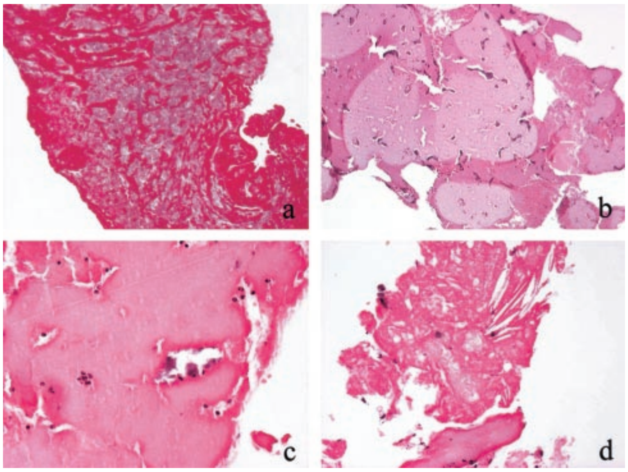

Figure 5. Microscopic view of retrieved material. a, Networks of fibrin strands. Azan stain; original magnification, ×40. b, Fragment is composed primarily of platelets. Hematoxylin-eosin stain; original magnification, ×25. c, Small calcific fragment within fibrin-platelet material. Hematoxylin-eosin stain; original magnification, ×40. d, Typical cholesterol needles within atheromatous gruel. Hematoxylin-eosin stain; original magnification ×31.

TABLE 5. Composition of the Retrieved Material at Microscopic Evaluation in Patients With Stable and Unstable Angina

	Stable Angina	Unstable Angina	*P*
Thrombus, %	69.6±7.2	78.9±16	NS
Plaque, %	30.4±7.2	21.1±16	NS

coronary syndromes undergoing percutaneous interventions, a larger amount of plaque debris could be aspirated from the target vessel when no-reflow occurred. Although glycoprotein IIb/IIIa inhibitors have been shown to reduce the incidence of periprocedural myocardial infarction, pharmacological therapy cannot be expected to play a decisive role when large amounts of plaque material are embolized distally.

Practical Considerations

Because distal protection increases the cost and complexity of the procedure, it would be important to identify the patients and the lesions with the greater embolic potential that could benefit most from the use of those devices. According to our results, distal protection appears to be particularly useful in patients with unstable angina and in those of older age.

In our experience, the use of the Angioguard device in highly selected lesions was technically feasible and safe.

Study Limitations

The embolic fragments captured by the filter may underestimate the actual amount of embolizing material. Embolization may occur while the Angioguard device crosses the stenosis before the deployment of the filter. Moreover, some debris may pass through the pores of the filter or sneak through the filter and the vessel wall if the contact between the two is defective. In addition, embolizing material can enter side branches proximal to the filter.

The possibility cannot be excluded that some of the retrieved thrombotic material could have been produced inside the bag while the filter remains in the cardiovascular system. However, it is well known that the material dislodged during PCI is highly thrombogenic. This suggests a sudden activation of the coagulative cascade within the PCI procedure at the plaque site rather than a later activation inside the filter.

The study was performed in a relatively small group of selected patients, and no control group was provided. Therefore, the clinical role of distal protection with filter devices has to be confirmed by further controlled studies enrolling larger patient cohorts.

Conclusions

Distal protection during percutaneous coronary artery intervention may limit embolization of atherosclerotic debris potentially able to wedge into small vessels and to cause myocardial injury. Our data support the use of distal protection devices especially in lesions with greater embolic potential, such as unstable plaques, and lesions in older patients.

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