

Embolic Protection With Filtering or Occlusion Balloons During Saphenous Vein Graft Stenting Retrieves Identical Volumes and Sizes of Particulate Debris

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Background—Distal embolization of plaque particulate liberated during stenting may cause periprocedural complications. The number, size, and volume of debris released during stenting, however, have not been quantified, rendering embolic protection approaches empiric. We used a novel method of microparticle size assessment to measure volume and characterize individual sizes of particles captured by the PercuSurge GuardWire balloon or a vascular filter during saphenous vein graft stenting.

Methods and Results—Braided nitinol filters (average distal pore size 100 μm) were used in 47 saphenous vein grafts in 44 patients. The PercuSurge GuardWire was used in 17 saphenous vein grafts in 16 patients. Particulate debris was subjected to microparticle size analysis (RapidVue, Beckman Coulter). All samples contained particulate debris. For both filter and GuardWire populations, most particles were $<100 \mu\text{m}$ in longest dimension (87% and 90% of particles, respectively), and the distribution of particle sizes was identical. Total embolic load per lesion for both filters and GuardWire aspirates was also similar: median embolic load per filter was 16 mm^3 (range 2 to 84 mm^3). Median embolic load per GuardWire was also 16 mm^3 (range 7 to 42 mm^3). Histopathologic analysis demonstrated that most samples contained plaque elements and platelet-rich thrombus.

Conclusions—During saphenous vein graft interventions, particulate retrieved with a vascular filtering device or an occlusion balloon was similar in amount and character. This supports the notion that unless soluble mediators play an important role in adverse acute clinical events after stenting, the clinical efficacy of filtering devices may be equal to that of occlusion devices. (*Circulation*. 2004;109:1735-1740.)

Key Words: bypass ■ embolism ■ myocardial infarction ■ stents

A major complication of percutaneous interventions in degenerated saphenous vein grafts (SVGs) is distal embolization of plaque constituents that results in no-reflow, myocardial infarction, and stroke.¹⁻³ Pharmacological approaches such as glycoprotein IIb/IIIa inhibition or direct stenting have not been shown to reduce complications resulting from distal embolization in SVG stenting.⁴⁻⁷ Distal protection devices⁸⁻¹⁷ have been developed, intended to trap plaque-derived emboli during interventions and prevent embolization into the distal vascular bed. There has been substantial debate surrounding the size and volume of particulate debris and the clinical relevance of large and small particles, as well as of soluble mediators generated during angioplasty and stenting. The first distal protection device evaluated clinically after SVG stenting, the PercuSurge GuardWire (Medtronic Inc), despite complete occlusion of

the vessel during intervention with temporary cessation of flow, was shown to reduce the incidence of no-reflow by 67% and of in-hospital and 30-day major adverse cardiac events by 42%.¹⁸ By virtue of complete occlusion and poststenting complete graft evacuation, the PercuSurge device theoretically prevents embolization of all particles, no matter how small, as well as of soluble mediators released during stenting.

It has not been established that the efficacy of occlusion systems can be matched by newer approaches to embolic protection such as filtering devices, which do not occlude antegrade flow but rather strain the effluent so as to prevent particulate embolization. Potential advantages of filtering include perfusion during intervention and shorter procedure times. Potential disadvantages include incomplete protection from emboli or failure to protect against soluble mediators. Both occlusion balloons and filters have the potential to inflict

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damage to the vessel wall during deployment, use, or retrieval. The recently published FIRE trial (FilterWire EX Randomized Evaluation) showed parity in clinical outcomes after SVG stenting in patients randomly assigned to embolic protection with the FilterWire (Boston Scientific) or to the GuardWire (Medtronic).¹⁹ However, rigorous particulate analysis was not performed in that trial, and it is not known whether there may be benefits of an occlusion balloon system (eg, more complete particulate retrieval and prevention of soluble mediators released during intervention) that are being offset by requisite procedural ischemia provoked by occlusion.

We used a filter constructed of braided nitinol with a distal pore size of 100 μm and the GuardWire to quantify and characterize the volume and individual sizes of particles captured during SVG stenting, postulating that particulate retrieval with the filter would be less efficient than with the GuardWire. Using novel methods of microparticulate quantification, we found that most particles released during SVG stenting were small ($<100 \mu\text{m}$) and that, contrary to our hypothesis, the vascular filter trapped even very small particles in equal amounts to the GuardWire.

These clinical data support the potential role for vascular filters in the efficient prevention of distal embolization during SVG interventions. Although only direct comparisons of clinical end points can prove equivalence, our data suggest that filters may be as effective as occlusion balloons. Furthermore, the abundance of small particles retrieved from SVG interventions will need to be compared with particulate debris retrieved from other vascular beds, eg, carotid, coronary, and renal, to optimize embolic protection device design and use in these locations.

Methods

Clinical Samples

Forty-seven filters from 44 patients entered in the Safety of Embolic Capture Utilizing the Medtronic AVE Distal Protection Device in Revascularization of SVGs (SECURE) study¹⁶ were submitted for analysis. Patients undergoing multiple SVG interventions had a new filter used for each SVG. The Medtronic filter (Medtronic/AVE) is a nitinol mesh basket attached to an 0.014-in guidewire. Initially constrained within a delivery sheath, once passed through the lesion into the distal SVG, the filter passively expands as the sheath is withdrawn. After stenting, the sheath is readvanced, and the filter is mechanically collapsed and withdrawn. After retrieval, each filter was immediately placed in 10% buffered formalin.

GuardWire samples were obtained from 16 consecutive patients undergoing protected stenting of 17 SVGs at Brigham and Women's Hospital. Forty milliliters of blood aspirated via the Export catheter was passed through the Becton Dickinson Cell Strainer 40- μm mesh filter, which was then placed into 10% formalin. For the single patient undergoing multiple-SVG intervention, the aspirate from each SVG was analyzed separately.

Particulate Isolation

Medtronic Filter

All material in the collection vial was analyzed, including debris in the filter and loose in the formalin. Filters (Figure 1) were placed in 0.01 mol/L PBS, filter wires were cut, and particulate was displaced into surrounding PBS via gentle agitation. Loose particles in formalin were collected with 2- μm filter paper and combined with particulate isolated from the filter, then placed in PBS. Control samples consisted of unused filters ($n=6$) processed in the same manner as the clinically used filters.

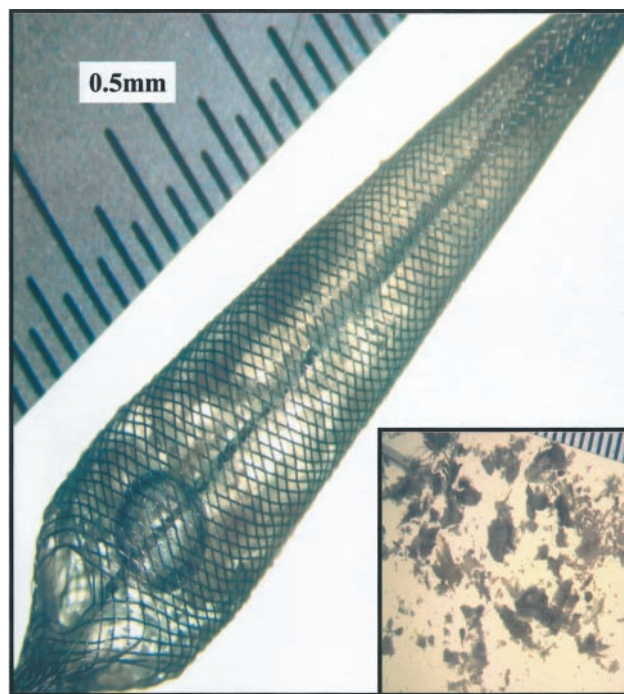


Figure 1. Nitinol filter after use in SVG stenting procedure. Particulate is visible throughout filter cavity. After liberation from filter (inset), particles are freely suspended before size analysis.

GuardWire Aspirate

All material aspirated during intervention on a given lesion was fixed in 10% buffered formalin and analyzed.

Particulate Analysis

The Coulter RapidVue apparatus was calibrated with National Institute of Standards and Technology-certified spheres ($200 \pm 4 \mu\text{m}$; Duke Scientific Co) before automated sample analysis. Aggregate particle volume measurements were validated in a separate experiment with poly(vinyl alcohol) (PVA) particulate (71% PVA 50 and 29% PVA 100, Cook Inc) to verify accuracy. Each sample was transferred to the RapidVue, and PBS was added to bring the total sample volume to 75 mL. Samples received in volumes >75 mL were divided into 2 parts and run separately, and the results were summed.

The closed-circuit RapidVue system circulated the particles and captured digital images at an automatically variable frame rate optimized for volume quantification as all particles passed through a field of view over 100 seconds (frame rates: GuardWire 5.30 to 26.19 frames/s; filter 6.84 to 26.67 frames/s; control 25 to 28.05 frames/s). Frame rate was inversely proportional to particulate quantity. These optimized parameters were used for all samples to allow direct comparison of results.

Samples were analyzed 3 times each to ensure repeatability, then retained for histological analysis. The results of the 3 runs per sample were averaged to obtain volume and size distribution data. Particle sizes were calculated with the least bounding rectangular (LBR) model, which gave the major and minor axes (Figure 2). Particle sizes were collated by major-axis measurement with categories previously appearing in the literature ($<56 \mu\text{m}$, 56 to 96 μm , 96 to 213 μm , 213 to 763 μm , and $>763 \mu\text{m}$).²⁰ Total volume of particulate for each sample was calculated as the LBR-derived volume output from RapidVue after 100 seconds (as determined by total volume calibration with PVA particulate) minus the volume calculated after 100 seconds for 6 control unused filters.

Histological Analysis

After particulate analysis, specimens were transferred into 70% ethanol, filtered into biopsy bags (Thermo Shandon), processed by a

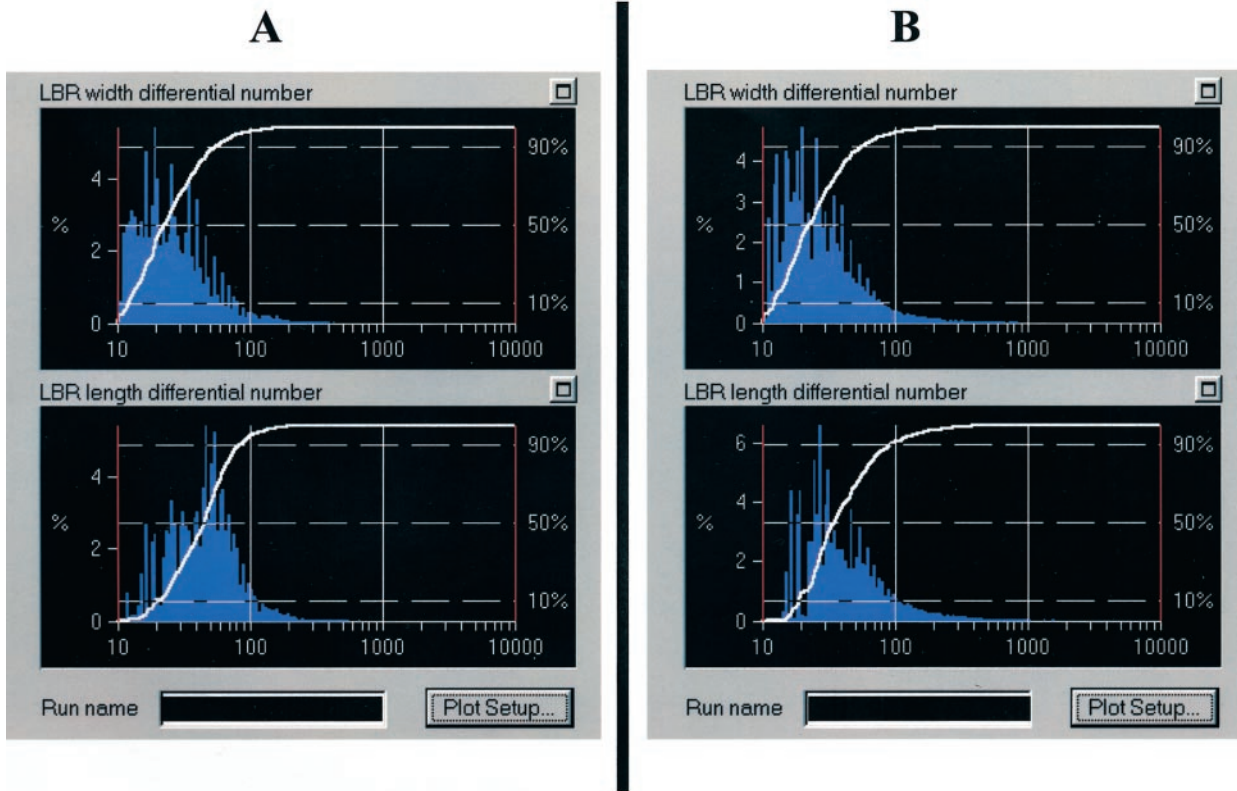


Figure 2. Particle size distribution plots for particulate retrieved during SVG stenting via GuardWire (A) or nitinol filter (B). x-axis units are length (μm); y-axis units are percent of particles. Upper plots are width of LBR; lower plots are length of LBR.

routine biopsy processing schedule, and embedded in paraffin. Serial 5- μm sections step-cut at 50- μm levels were collected and stained with Mayer's hematoxylin and eosin-Y. Representative levels in particulate specimens were also stained with Carstairs' fibrin stain and with picosirius red for collagen. Immunohistochemical staining was performed to label CD68 (clone: PG-M1, Dako Co) for monocyte/macrophages and smooth muscle cell α -actin (clone: 1A4, Dako Co) for smooth muscle and fibromuscular cells with the EnVision+ detection system (Dako Co). Stained sections were viewed and qualitatively scored blindly, and scored sections were sorted on the basis of the presence of tissue components into 3 groups: (1) thrombus with plaque elements (containing white thrombus, foam cells, and fibrous plaque elements), (2) thrombus only (containing either white or red-cell and white thrombus), and (3) no visible material.

Statistical Methods

Data are presented as median and range values. Comparisons between filter and GuardWire volumes and between particle size distributions for filter and GuardWire samples were performed with nonparametric statistics (2-tailed Mann-Whitney U test) rather than parametric statistics because the data were likely not normally distributed. $P < 0.05$ was considered significant. To estimate the statistical power of this study, the differences detectable with 80% power between the 2 samples were estimated for volume and particle dimensions (major and minor axis) with parametric statistics (mean and SD estimates). Because the data are slightly right-skewed for all measurements and deviate somewhat from normal distribution, these power estimations are not exact.

Results

Calibration With Microspheres

NIST-certified beads ($200 \pm 4 \mu\text{m}$) were placed in a 75-mL volume of PBS for RapidVue analysis. The beads were

analyzed 4 times. The RapidVue-calculated bead size was compared with the NIST-certified size range of the beads, and the results (198.2 to 200 μm) were within the certified range.

Total Volume Calibration With PVA

Samples with known volume (5, 10, 30, 50, 70, or 100 mm^3) and size distribution (71% PVA 50 and 29% PVA 100) of PVA particulate were measured in the RapidVue. Seven samples of each volume were used, and each sample was run 3 times. The RapidVue volume calculations (5 mm^3 : $6.79 \pm 1.2 \text{mm}^3$; 10 mm^3 : $12.80 \pm 1.08 \text{mm}^3$; 30 mm^3 : $29.05 \pm 2.26 \text{mm}^3$; 50 mm^3 : $53.03 \pm 9.86 \text{mm}^3$; 70 mm^3 : $64.88 \pm 5.95 \text{mm}^3$; and 100 mm^3 : $92 \pm 7 \text{mm}^3$) were comparable to the known volumes after 100 seconds.

Particle Size Distribution

Mean and median particle sizes of debris captured with filters or with GuardWire were nearly identical (filter: mean $62.9 \pm 13.2 \mu\text{m}$ [median 59.4 μm] in major axis, mean $34.7 \pm 4.8 \mu\text{m}$ [median 34.8 μm] in minor axis; GuardWire: mean $59.8 \pm 13.4 \mu\text{m}$ [median 55.4 μm] in major axis, mean $38.2 \pm 7.6 \mu\text{m}$ [median 34.8 μm] in minor axis, $P = 0.28$). Particle size distributions were also nearly identical for filter and GuardWire samples (<56 μm in longest dimension: $70.5 \pm 6.7\%$ [median 70.9%] of particles from each filter, $64.7 \pm 13.0\%$ [median 68.2%] of particles from each GuardWire sample; and 56 to 96 μm in longest dimension: $16.8 \pm 2.7\%$ [median 16.6%] for filters and $25.3 \pm 9.2\%$ [median 24.9%] for GuardWire samples; Figure 3). The largest

Size Distribution of Particle Longest Dimension

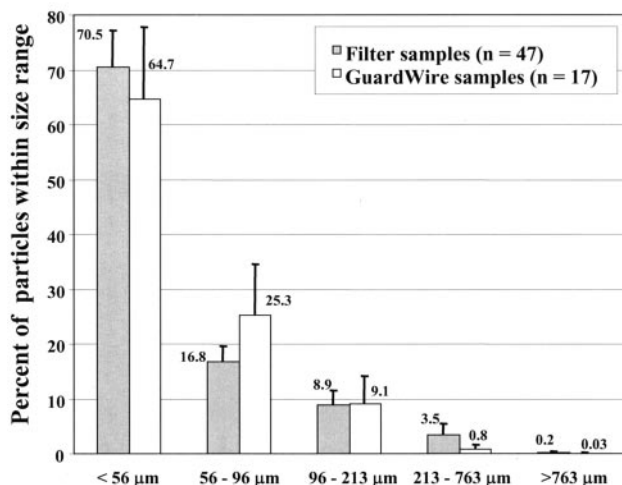


Figure 3. Size distribution of particulate retrieved from SVG stenting procedures via nitinol filter (solid bars) or GuardWire (open bars). Size partitions were chosen to match those reported previously for GuardWire embolic protection. No difference was observed in particulate size distribution between filter and GuardWire. Despite nominal distal pore size of 100 μm, filters trapped emboli far smaller than 100 μm in longest dimension.

particles retrieved were 2148 μm with the GuardWire and 2980 μm with the filter in the longest dimension.

Total Volume Distribution

Total embolic load per lesion for filters and GuardWire samples was similar (GuardWire: mean 17±9 mm³ [median 16 mm³, range 7 to 42 mm³]; Filter: mean 23±19 mm³ [median 16 mm³, range 2 to 83 mm³]). A box plot comparison (Figure 4) demonstrated identical median values and a larger range for the filter that correlated with its larger sample (GuardWire n = 17, filter n = 47).

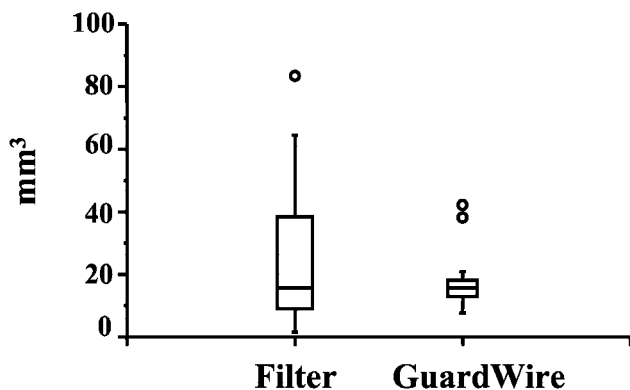


Figure 4. Total volume by device showing similar expected values of retrieved debris. Median values (horizontal bar within box) were identical (16 mm³), and wider range of interquartile difference (width of 25th and 75th percentile boundaries, shown as lower and upper box edges) for filter correlated with its larger sample (GuardWire n = 17; filter n = 47). Whiskers above and below boxes extend to furthest points within 1.5 interquartile range above and below box edges, and open circles mark outlier values.

Statistical Power to Detect Differences

Given the sample size of each group and variance estimates observed, the present study had 80% power to detect a difference between the 2 groups of 16.8 mm³ in volume, 6.1 μm in the mean minimum-axis dimension, and 10.5 μm in the mean major-axis dimension.

Histological Evaluation

The histological assessment of particulate tissue obtained from 47 filters revealed that the braided filter contained thrombus together with plaque elements in 18 samples (38%) and thrombus alone in 23 samples (49%). Among the 17 GuardWire aspirate samples, thrombus together with plaque elements was seen in 5 samples (29%) and platelet-fibrin rich thrombus in 8 samples (47%).

No tissue was seen in 6 filter samples (13%) and 4 GuardWire samples (23%), likely related to loss of particles during processing for histological analysis after particle size analysis, because inspection of particulate after RapidVue analysis showed gross visualization of particulate from all filters and GuardWire aspirates. Similar rates of loss during handling have been reported previously.⁷

Discussion

Acute myocardial infarction occurs after SVG stenting in 15% to 28% of cases,^{13,21-23} often preceded by reduced intraprocedure flow despite adequate mechanical treatment of stenoses (no-reflow). Late morbidity and mortality are higher in patients who have a myocardial infarction after SVG stenting than in those who do not.²⁴ Etiologic possibilities include soluble mediators released from red blood cells, platelets, or leukocytes during stenting, acutely dislodged plaque elements, and delayed embolization of plaque or thrombotic elements. Pharmacological strategies proposed to prevent or treat periprocedural no-reflow have included calcium channel blockers, nitrates, adenosine, thrombolytics, and antiplatelet agents. A registry reported from Brigham and Women's hospital²⁵ demonstrated that despite improving angiographic flow, antiplatelet and vasodilatory agents were not associated with improved clinical outcomes. Mechanical strategies proposed to prevent no-reflow have included direct stenting and the use of high surface-coverage stents or covered stent grafts to trap debris against the vessel wall.

Distal balloon occlusion during stenting with subsequent aspiration of dislodged debris is the only approach to date shown to limit adverse clinical events and angiographic no-reflow after SVG stenting. In the SAFER trial (Saphenous vein graft Angioplasty Free of Emboli Randomized trial), patients undergoing SVG stenting and randomly assigned to distal embolic protection with the PercuSurge GuardWire system had a 42% reduction in risk of periprocedural adverse cardiac events, primarily myocardial infarction.¹⁸ Despite the marked efficacy of occlusive distal protection, however, its widespread adoption has been limited. Clinical tolerance of occlusion is not universal, fluoroscopic visualization of stenoses before and after stenting is limited, and in vascular beds other than SVGs, the inability to protect proximal side branches from embolization limits the efficacy of distal balloon occlusion. Vascular filtering devices may offer supe-

riority over occlusion devices in ease of use, patient tolerance, visualization, and proximal side-branch protection. On the other hand, filters may not be able to trap small fragments and certainly cannot prevent soluble mediators from reaching the distal vascular bed.

The randomized FIRE trial showed similar clinical efficacies of balloon occlusion and filter protection with the FilterWire (Boston Scientific) during SVG stenting¹⁹ (major adverse cardiac events occurred in 9.9% of FilterWire patients and 11.6% of GuardWire patients; $P=0.0008$ for noninferiority of the FilterWire). Importantly, that study did not examine mechanistic underpinnings of device efficacy, capture efficiency, or adverse events. For example, one might view the clinical equivalence demonstrated in FIRE, which used a filter with a nominal pore size of 110 μm , as an indication that particles smaller than 110 μm are unimportant in the genesis of adverse events after SVG stenting. However, without examining the particulate retrieved via filters or occlusion systems, such a conclusion would be speculative.

Previous analyses of embolic particulate liberated by arterial stenting have used scanning electron or light microscopy²⁰ to measure manually the size of a subset of retrieved particulate but have not quantified retrieved particulate volume for relative comparison between occlusive and filtering distal protection techniques. Grube et al²⁰ reported that >80% of particles retrieved with the GuardWire from SVG stenting were <96 μm in largest dimension, which lends strength to the notion that filters may afford less complete protection, because smaller particles might pass through unimpeded.

We constructed the present data analysis to conform to the size categories reported by Grube et al,²⁰ and our data from GuardWire cases are virtually identical to theirs, which validates our measurement technique. The present study applied a highly sensitive and reproducible microparticle size analysis system to debris retrieved from SVG stenting procedures with GuardWire occlusion or with a vascular filtering device (average distal pore size 100 μm). We found that a vascular filter with a nominal distal pore size of 100 μm captured particles far smaller than 100 μm and retrieved the same total volume of particulate as a device that achieved complete occlusion. One possible explanation is that deposition of aggregate debris, platelets, or fibrin on the filter pores reduces the functional orifice size. Another is that debris adheres to the surface of the filter and is thereby prevented from distal embolization.

The connection between retrieved particulate and the prevention of embolism-related adverse clinical events (no-reflow and myocardial infarction) remains to be proven. In the present study, there were no in-hospital deaths or Q-wave myocardial infarctions in either group. No-reflow occurred in 5.3% and non-Q-wave myocardial infarction during hospitalization in 7.0%¹⁶ of filter-treated patients. Non-Q-wave myocardial infarction occurred in 6.0% of the 16 patients treated with the GuardWire. These incidence rates compare favorably with the 30-day event rates among patients who received distal embolic protection in the FIRE and SAFER trials.

Most explorations of distal embolic protection have involved degenerated SVGs. Native coronary occlusions in the

setting of acute myocardial infarction and carotid²⁶ and renal artery stenoses are also potential sites where distal embolization during intervention exacts a clinical price. Debris released in these settings may differ from SVG debris in quantity, histopathologic composition, and total volume. Particulate analysis will be an important element in determining optimal device selection and design for each clinical setting.

Study Limitations

The present data are nonrandomized, derived from 2 sets of patients undergoing SVG stenting. Therefore, the embolic loads liberated during stenting may have differed, although there were no selection criteria for filter patients that would make them particularly different from GuardWire patients. Specimen handling also varied slightly between groups: the filter group had the filter collapsed and withdrawn at the end of the procedure, whereas the GuardWire group had the sample aspirated via the Export catheter, then sieved with a 40- μm mesh. This difference could alter particulate size via compression or fragmentation of particles, although the data from the present study indicating that particulate volume and size distribution were essentially identical between devices are reassuring. Similarly, particles may have been liberated before or during deployment, may have escaped capture, and thus may not be analyzed. Finally, the lower limit of detection for the RapidVue is 10 μm . Fragments smaller than 10 μm might be captured more reliably by one system or the other, although a clinical effect of such erythrocyte-sized particles is unlikely.

Conclusions

Liberation of atherosclerotic plaque elements during vascular interventions may be universal and unavoidable and may be an important cause of periprocedural adverse events. Novel approaches to embolic protection, specifically vascular filtering rather than occlusion, have been hampered by the notion that some fragments will escape capture and cause adverse events. The present data suggest that filtering may be as efficient as balloon occlusion at particle capture, despite pore sizes larger than the vast majority of particles. This observation may help justify the application of existing technologies and direct future development optimizing safety and efficacy in diverse settings where procedurally induced plaque embolization occurs.

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