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# The Incidence of Emboli during Cardiac Surgery: A Histopathologic Analysis of 2297 Patients

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## ABSTRACT

**Objective:** Manipulation of the atherosclerotic aorta during cardiac surgery is assumed to cause embolization, which can contribute to adverse outcomes. Recently, as a result of worldwide trials deploying the Embol-X intraaortic filter during cardiac surgery, such emboli were captured and processed for histopathologic analysis.

**Methods:** Filters with a pore size of 120 microns were placed in 2297 patients who underwent the following operations: coronary artery bypass grafting (CABG) (70%), valve (17%), combination CABG/valve (11%), and other (2%).

**Results:** The filters captured at least one embolus in 98% of the patients. An average of 8.3 particles was captured per filter (range of 0-74). The surface area of the emboli was on an average 5.8 $mm^2$ (range of 0-188 $mm^2$). Histologic analysis of the captured particles indicated that in 79% of the filters fibrous atheromata were noted, in 44% there were platelets and fibrin, 8% had red blood cell thrombus, 3% had fibrofatty/adventitial tissue, 2% had other material including cartilage, myocardium, lung, suture, and a teflon pledget. Of the patients enrolled, 1569 were high-risk. The average number of particles captured in the high-risk patients was 8.5 versus 5.8 for the low- to moderate-risk patients ($P < .0001$). Concomitantly, there was an increase in the embolic burden between the higher- and lower-risk patients (surface area 6.6 vs. 4.0 $mm^2$, $P < .0001$).

**Conclusion:** These data show the ubiquitous incidence of emboli during cardiac procedures. Intraaortic filtration should reduce adverse outcomes as was demonstrated for the high-risk patients in this study.

Aortic manipulation during cardiac surgery can cause embolization and increase morbidity. The use of an intraaortic filter can decrease the embolic burden. We now report the histopathologic analysis of these emboli.

## INTRODUCTION

One of the limitations of cardiac surgery continues to be the morbidity of the procedures. Despite successful efforts to decrease this morbidity in a patient population of increasing risk, there remain significant complications that occur [Ferguson 2002]. The correlation of postoperative complications and aortic atheromata has been established [Blauth 1992, Calafiore 2002, Doty 2003, Davila-Roman 1991, Wareing 1992]. Manipulation of such aortas results in embolization that can lead to devastating adverse outcomes such as stroke and renal failure [Barbut 1997, Davila-Roman 1999, Doty 2003, Wareing 1992]. The true frequency of embolization is unknown and is inferred by complication rates. Recently, an intraaortic filter was developed to prevent such complications and has been employed worldwide since 1999 [Banbury 2003, Bergman 2002, Harringer 2000, Reichenspurner 2000, Schmitz 2001, 2003, Wimmer-Greinecker 2003]. The clinical results from these randomized and nonrandomized trials have been previously described. The purpose of this report is to focus on the histopathologic analysis of the emboli captured to describe their characteristics and document their incidence in the combined clinical population. Additional analysis of the correlation between embolic capture and preoperative risk factors helped identify the patients who would receive the greatest benefit from intraaortic filtration.

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## MATERIALS AND METHODS

### *Patients*

From January 1999 to February 2002, 2373 patients underwent cardiac surgery with the deployment of the Embol-X Intraaortic Filtration System. These patients were treated at 39 different institutions from nine different countries in Europe and North America. A total of 1645 patients were enrolled in a prospective, consecutive enrollment registry in Europe and the remaining 728 patients represented the roll-in and treatment arm of a randomized controlled trial in the USA. The inclusion criteria for the randomized controlled trial were patients, 60 years of age and older, who were undergoing for the first time, nonemergent isolated CABG or isolated valve repair/replacement. The registry included patients undergoing initial or reoperative cardiac surgery, or CABG, valve, or combination CABG/valve procedures. The registry also included emergency operations and patients 18 years of age or older. Patients with ascending aortic aneurysms or trauma were not treated with filtration. Patients in whom the filter was lost to examination ($n = 76$) were excluded from analysis in the registry, leaving a total of 2297 patients receiving the filter for histologic analysis.

Figure 1. Photograph of Embol-X cannula and filter system. The filter is in the deployed position as it would be for intraaortic filtration.

Table 1. Baseline Demographics

| Preoperative Characteristics | Patients n (%) |
|---|---|
| Age ≥60 | 1944 (85) |
| Hypertension | 1501 (66) |
| Hypercholesterolemia | 1299 (57) |
| Left main disease | 525 (23) |
| MI (>7 days preop) | 514 (22) |
| Diabetes | 491 (21) |
| Unstable angina | 376 (16) |
| Atrial arrhythmia | 351 (15) |
| Obesity | 314 (14) |
| Peripheral vascular disease | 312 (14) |
| Smoker | 286 (12) |
| Acute MI (<7 days preop) | 254 (11) |
| Renal dysfunction | 223 (10) |
| Aortic disease | 220 (10) |
| Congestive heart failure | 218 (10) |
| Carotid stenosis | 217 (9) |
| TIA | 129 (6) |
| Stroke | 122 (5) |
| Ventricular arrhythmia | 92 (4) |
| Low cardiac output | 69 (3) |
| Alcohol abuse | 51 (2) |
| Hepatitis | 37 (2) |
| Cerebrovascular surgery | 49 (2) |
| Neurocognitive deficit | 33 (1) |
| Endocarditis | 27 (1) |
| Cardiogenic shock | 18 (1) |

### *Intraaortic Filter Device*

The Embol-X Intraaortic Filtration System (Embol-X System, Edwards Lifesciences, Irvine, CA) is comprised of a collapsible filter that is inserted into the aorta through the side port of a 24F metal-tipped intraaortic cannula (Figure 1). The filter is made of a heparin-coated polyester mesh with a pore size of 120 microns. A flexible wire frame allows the filter to conform to the internal diameter of the aorta. In all cases, the filter was deployed just prior to the release of the cross-clamp and was left in the ascending aorta until the patient was weaned from cardiopulmonary bypass. Once the filter was removed, it was visually inspected for captured debris. The filters and debris were then fixed in formalin and submitted to a central histopathology core laboratory (G.B., Stanford University, Stanford, CA) for analysis. At 10× magnification, the quantity and size of the captured particles were determined. Further staining with hematoxylin and eosin, trichrome, and Elastica van Gieson of particles was also performed. Once the particles underwent a histologic analysis, a subset of the filters and particles underwent a scanning electron microscopic analysis at 20×, 100×, and 500× for the particles and at these magnifications as well as at 1000× for the filters. Identification and description of the particulate material was recorded. Since multiple particles could be captured per filter, the histologic nature of these particles could also be of multiple origins.

### *Statistical Analysis*

The analyses were performed on the filter treatment arm of the randomized trial and the registry patients where a filter was used. Categorical variables were compared using Pearson's chi-square or Fisher's exact test for variables with very low frequencies. Continuous variables were compared using two sample *t* tests. If any difference was found to be nominally significant at the 10% level, it was then included in subsequent analyses of the primary safety variable. All statistical analyses were performed using the SAS version 8.2 (SAS Institute, Carey, NC).

### *Results*

Table 1 demonstrates the patient characteristics. As the majority of the patients undergoing cardiac surgery were on CABG procedures, the demographics reflect the population of such patients. It is to be noted that the combined incidence of preoperative stroke, TIA, or neurocognitive deficit was 12%, which is slightly higher than what is typically reported from regional and national databases. Similarly, the degree of preoperative renal dysfunction is also slightly elevated at 10%.

Table 2 documents the type of procedures that were performed. As mentioned, the majority of these were CABG operations. Of note, and illustrative of the ability to use intraaortic filtration without cardiopulmonary bypass is the fact that 47 patients underwent off-pump CABG with intraaortic filtration performed during the creation of the proximal anastomoses, while a partial occluding clamp was placed on the ascending aorta.

The average cross-clamp time for all operations was 66 minutes (range 10-205 min). The average filtration time was 29 minutes with a range of 20 seconds to 187 minutes.

Table 2. Type of Procedures Performed*

| Operative Characteristics | Patients n (%) |
|---|---|
| CABG | 1560 (68) |
| Off-pump | 47 (2) |
| Valve repair/replacement | 379 (17) |
| CABG/valve | 246 (11) |
| Other | 45 (2) |
| Prior CABG or valve surgery | 80 (3) |
| Preop status | |
| Elective | 1831 (80) |
| Urgent | 315 (14) |
| Emergency | 25 (1) |

*CABG indicates coronary artery bypass grafting.

### *Morbidity and Mortality*

The outcomes of the observations made on these patients have previously been reported [Banbury 2003, Schmitz 2001, 2003, Wimmer-Greinecker 2003]. The overall mortality rate was 2.8%. There was a 1.7% incidence of stroke and 0.5% incidence of TIA. Renal insufficiency, defined as serum creatinine greater than 2 mg/dL or 50% increase over the baseline, was observed in 4% of the patients. As previously shown, the clinical safety of the filter device was demonstrated with no difference in the overall observed mortality from the expected mortality based on a previously reported logistic regression analysis [Banbury 2003, Wimmer-Greinecker 2003]. Internal verification of these endpoints was also made in the 645 patients enrolled in the randomized controlled trial who did not incur a higher mortality rate than those in the control (nonfiltration patients) from the randomized controlled trial [Wimmer-Greinecker 2003]. With regard to morbidity, a composite endpoint event rate was also similar at 17% for the patients receiving the filter versus 19% for those who did not in the randomized trial.

### *Particulate Capture*

The average number of particles captured was 8.3 with a range of 0-74. The average surface area of the particles captured was 5.8 $mm^2$ with a range of 0-188 $mm^2$. The distribution of patients, according to the total surface area of all particles captured per filter, is depicted in Figure 2. As can be seen, 50% of the patients had particulate capture of a size greater than 3 $mm^2$. This represents the results from all patients, regardless of the type of operation. A breakdown of these results, according to the type of procedure, revealed no difference in this distribution whether the operation was a CABG, valve, or a combination. The number of particles and surface area did not vary with respect to the type of operation performed.

It may be noted that in the randomized controlled trial, the use of a partial occluding clamp on the aorta was monitored. There was a significant increase both in the number of particles captured associated with the use of the partial clamp (average 6.3 versus 5.4, range 0-18 versus 0-38, $P = .014$) and in the total surface area of the particles captured (5.0 versus 3.2 $mm^2$, $P = .013$).

### *Histology and Scanning Electron Microscopy*

The pathologic identification of the captured particulate emboli was performed by an independent cardiac pathologist core lab (Stanford University Medical Center). Gross, light microscopy and scanning electron microscopy analyses were

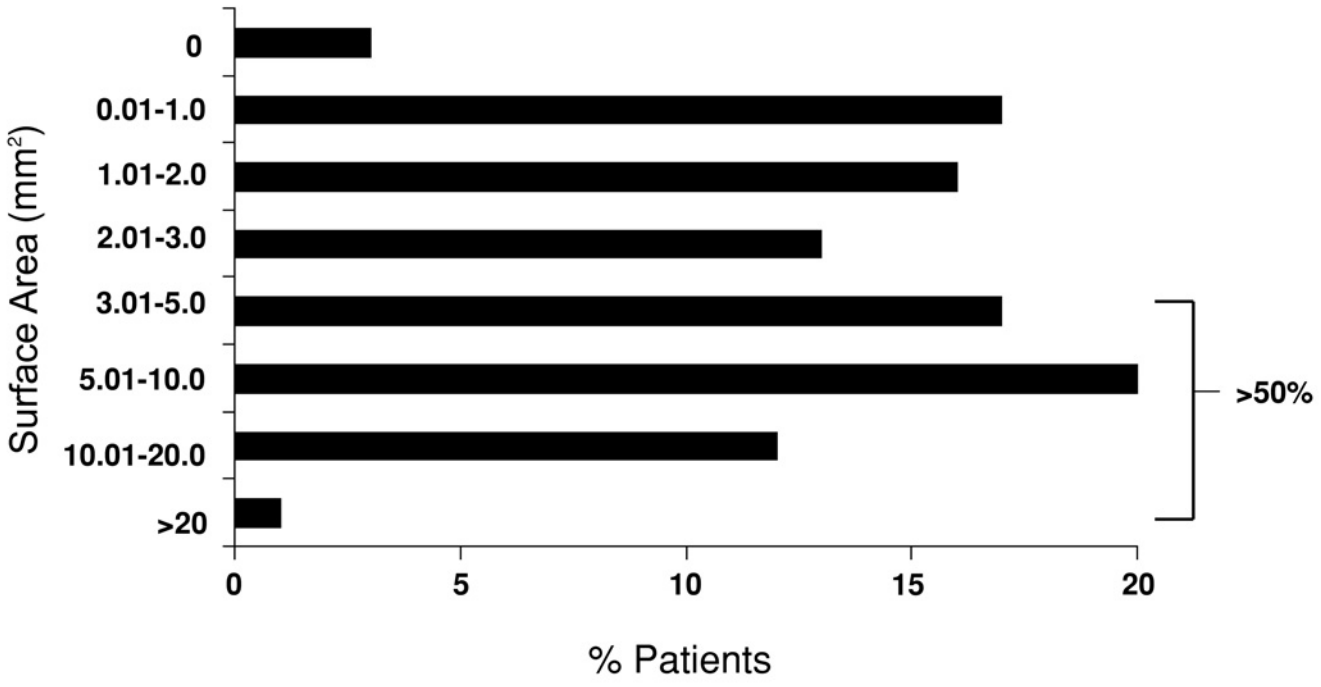


Figure 2. Distribution of patients according to the surface area of emboli captured in each patient. Over 50% of the patients had emboli measuring >3 $mm^2$.

Table 3. Histopathology Results

| | |
|---|---|
| Fibrous atheroma | 79% |
| • Fibro calcific atheroma | 5% |
| • Grumous atheroma/cholesterol | 2% |
| Platelets/fibrin | 44% |
| RBC thrombus/clot | 8% |
| Fibrofatty/adventitial tissue | 2% |
| Medial tissue | 1% |
| Non vascular/foreign body* | 2% |

*Includes suture material, adipose tissue, lung, cartilage, fungus, and teflon pledget.

performed. Table 3 delineates the results of these analyses. The total of the percentages listed in Table 3 is greater than 100 since multiple particles were captured per filter, and the particles could be of multiple etiologies. As noted, the vast majority of the particles were fibrous atheromata. However, there was a significant number composed of platelets and fibrin. Some of the largest individual specimens extracted were well-developed red blood cell thrombus, indicative of mural thrombi. Additionally, a potpourri of other material was captured, 2.3% (n = 53 filters), including cartilage, myocardium, adipose, lung, and foreign bodies such as suture and a teflon pledget. The only difference noted histologically was that fibrocalcific atheromata were more likely seen following valve procedures. Representative photographs of gross and microscopic pathology are displayed in Figure 3.

Scanning electron microscopy was performed to verify that the Embol-X aortic filter was not thrombogenic. A selected randomized evaluation of such filters showed no significant thrombogenic activity on the filter mesh. Minimal platelet aggregation was noted and there was no correlation between dwell time and amount of platelet aggregation.

### *High-Risk Patients*

Using a validated risk stratification scoring system [Higgins 1992], 1569 patients were considered to be high-risk, based on preoperative factors having a risk score of 5 or more (eg, such risk factors as age greater than 75 years, prior vascular surgery, vascular disease, diabetes, and LV dysfunction). The particulate capture rate for these high-risk patients was the same as for the moderate- to low-risk patients at 98%. However, the average number of particles captured in the high-risk patients was 8.5 versus 5.8 for the low- to moderate-risk patients ($P < .001$). Concomitantly, there was an increase in the embolic burden between the higher- and lower-risk patients (surface area 6.6 versus 4.0 $mm^2$, $P < .0001$).

## CONCLUSIONS

The correlation between manipulation of the atheromatous aorta and embolization-related adverse outcomes is established [Barbut 1997, Blauth 1992, Calafiore 2002, Doty 2003, Davila-Roman 1999, Wareing 1992]. Methods to deal with this problem in a patient population that carries an increasing burden of comorbidity into the operating room have proven difficult.

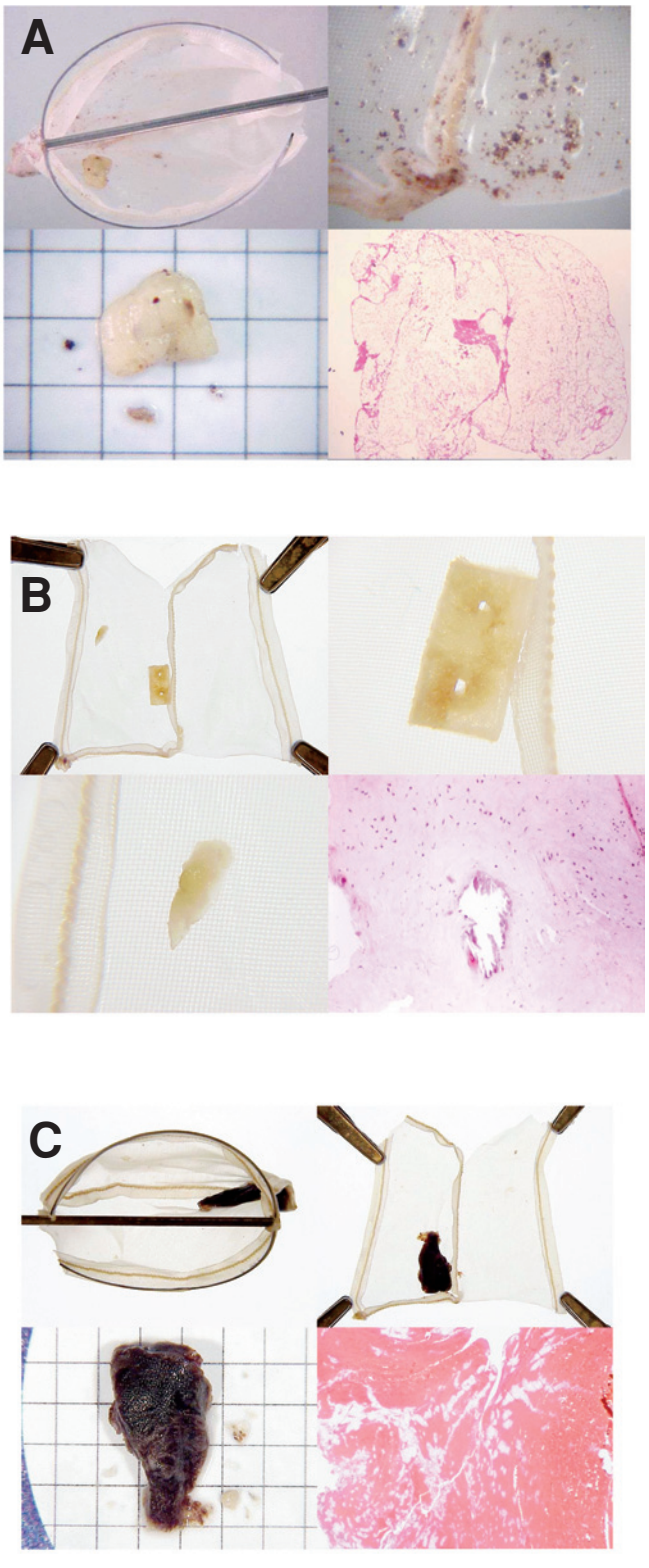


Figure 3. Gross and light microscopy (H&E, 100×) photographs of filters and emboli. Grid is 3 $mm^2$. A, Numerous captured emboli including a large piece of fibroadipose tissue; B, teflon pledget and fibrocalcific atheroma; and C, large red blood cell thrombus.

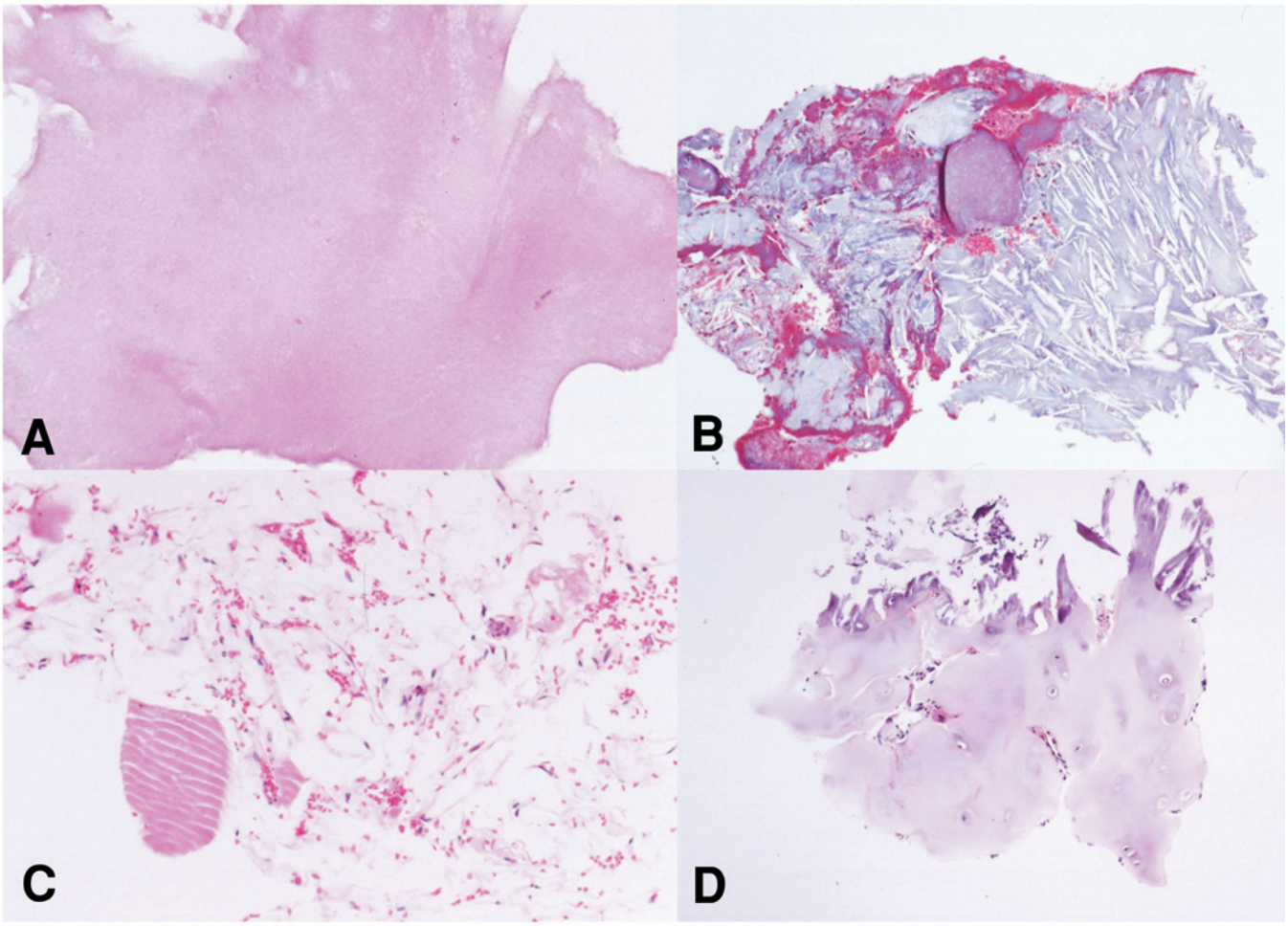


Figure 4. Photomicrographs of histology of emboli captured. A, Platelets and fibrin thrombus; B, mediastinal fibroadipose tissue; C, atheromatous core containing cholesterol clefts; and D, hyaline cartilage (100× magnification, a, b, d H&E; c trichrome).

The safety and efficacy of intraaortic filtration in cardiac surgery to ameliorate these complications have been studied and reported in nonrandomized and randomized trials [Banbury 2003, Bergman 2002, Harringer 2000, Reichenspurner 2000, Schmitz 2001, 2003, Wimmer-Greinecker 2003]. As a result of these trials, over 2000 filters have been deployed, and at a rate of 98% these filters have captured emboli. The ubiquitous prevalence of these emboli during all types of cardiac surgery is noteworthy. While this prevalence has been inferred from indirect measures such as the doppler signal [Barbut 1994] and autopsy findings [Blauth 1992, Wareing 1992], the origin(s) of these emboli have largely been assumed. This report documents the histopathologic analysis of these emboli as captured across a wide range of practices and sites (Figure 4). Not surprisingly, the majority of the emboli were atheromatous in nature. However, the incidence of platelet and fibrin emboli are of interest in understanding the interactions of these blood components as a source of atheroemboli. Additionally, the assortment of noncardiovascular tissue and foreign bodies, fortunately rare, should be noted.

The correlation between the use of a partial occlusion clamp on the aorta and an increase in the number and size of emboli released carries implications not only for on-pump, but off-pump cardiac surgery as well, where manipulation of the ascending aorta may still result in the release of atheroemboli. There exists a clinical observation that patients at higher preoperative risk tend to have more complications [Ferguson 2002]. The data from this study indicate that an underlying etiology for this may be the increased number and size of the emboli released into the bloodstream due to the increased degree of atheromatous disease seen in higher-risk patients. That over 98% of the filters captured one or more particles and that these particles are predominantly of atheromatous origin substantiates the role of atheroembolism in impacting clinical morbidity, as well as the filter's ability to reduce the embolic load. Recently, in a single-center study, a reduction in adverse neurologic outcomes was associated with the use of the filter compared to nonfilter patients (4.3% vs. 11.9%, $P < .001$) [Schmitz 2003]. In this study, logistic modeling demon-

strated that patients not receiving a filter may be 2.7 times likely to experience an adverse neurologic event.

Intraaortic filtration provides a means of capturing emboli of all types and in so doing, helps prevent adverse outcomes. The high incidence of emboli that were captured and removed by the filter increases in number in higher-risk patients, suggesting that many patients would benefit from intraaortic filtration and the largest benefit may be seen in patients with the largest risk.

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