International Council of Emboli Management (ICEM) Study Group results: risk adjusted outcomes in intraaortic filtration

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Abstract

**Background:** The Multicenter Study of Perioperative Ischemia (McSPI) developed and validated a Stroke Risk Index for estimating the likelihood that patients undergoing isolated coronary artery bypass grafting will experience major perioperative neurologic events. The International Council of Emboli Management (ICEM) Study Group has suggested that use of intraaortic filtration reduces adverse neurologic events. **Objective:** The objective of the present study was to compare predicted and observed neurologic outcomes in patients receiving intraaortic filtration. **Patients and Methods:** From February 1999 to August 2000, 962 patients were enrolled consecutively in a prospective, nonvoluntary registry of intraaortic filtration in 15 European centers. Of these, 447 underwent isolated coronary artery bypass grafting, the target population for applying the McSPI Stroke Risk Index. Forty-five had incomplete data, yielding a study group of 402 patients. The Stroke Risk Index was calculated for each patient, and the sum across patients yielded an expected number of neurologic events. These were compared to observed events by confidence limits and goodness of fit. **Results:** Six neurologic events were observed (1.5%; 95% confidence limits 0.6–3.4%), roughly half the 13.7 predicted by the Stroke Risk Index (3.4%; 95% confidence limits 2.0–5.8%), \(P = 0.03\). **Conclusions:** Adverse neurologic events associated with coronary artery bypass grafting in which intraaortic filtration was used were rare and fewer than expected on the basis of the Stroke Risk Index. Rare occurrence of clinically relevant events precludes their use as primary endpoints for randomized clinical studies; however, the Stroke Risk Index provides a valuable benchmark in the absence of such studies. © 2001 Elsevier Science B.V. All rights reserved.

**Keywords:** Intraaortic filtration; Neurologic outcomes; Stroke Risk Index; Coronary artery bypass grafting; Cardiopulmonary bypass

1. Introduction

The Multicenter Study of Perioperative Ischemia (McSPI) developed, validated and published a predictive Stroke Risk Index for patients undergoing isolated coronary artery bypass grafting using conventional cardiopulmonary bypass for support [1–3]. The McSPI Stroke Risk Index is intended to be applied preoperatively to estimate the likelihood that a patient will experience a major perioperative neurologic event.

The International Council of Emboli Management (ICEM) is a study group formed in 1999 to investigate the effects of intraaortic filtration during cardiopulmonary bypass. Beginning in February 1999, 15 European centers have enrolled consecutive patients in a prospective, nonvoluntary registry of intraaortic filtration (Embol-X\(^c\), Mountain View, CA, USA). This group has suggested that intraaortic filtration has reduced occurrence of adverse neurologic events [4,5]. However, to date, no randomized clinical trial of the efficacy of intraaortic filtration has been mounted.

In the absence of such a trial, the purpose of this study was to use the validated McSPI Stroke Risk Index to compare predicted to observed neurologic outcomes in patients enrolled in the ICEM registry.

2. Patients and methods

2.1. Patients

The ICEM study is an ongoing, prospective, nonvoluntary, consecutive enrollment registry of patients receiving...
intraaortic filtration. Between February 1999 and August 2000, 962 patients were enrolled. Of these 447 underwent isolated coronary artery bypass grafting (CABG). Excluded were patients receiving valve or combined CABG and intra-cardiac procedures, emergent patients, and patients receiving a concomitant carotid endarterectomy and CABG \((n = 515)\). Of the 447, 45 patients were excluded on the grounds of incomplete data, because it made meaningful application of the McSPI index impossible. Such cases included all patients missing age data or neurologic outcomes data; in addition, patients were excluded if they were missing more than two risk factors included in the Stroke Risk Index. Thus, the final study group included 402 patients.

2.2. Intraaortic filtration

All patients underwent coronary artery bypass grafting supported by conventional cardiopulmonary bypass and aortic cross-clamping. The intraaortic filter was placed in the aorta just prior to cross-clamp removal, and was removed when the heart was ejecting fully. The location of the filter was immediately distal to the cross-clamp, but proximal to the arterial return cannula and the innominate artery (see Fig. 1). Particulate matter (Fig. 2) was retrieved in most filters, and in over 65% of the filters, fibrous atheroma, including fibrocalcific and grumous material, was found \([4,5]\).

2.3. Definition of outcomes

Neurologic outcomes included stroke, transient ischemic attack (TIA), coma, or central nervous system (CNS) death for each patient as determined by the site investigator at each institution. These have been designated collectively as Type I events by the McSPI study group \([1,2]\). To match the neurologic outcomes modeled by the Stroke Risk Index investigators, other neurologic deficits such as deterioration in intellectual function, confusion, agitation, disorientation, memory deficit, or seizure were not considered unless a focal neurologic event was present. The events reporting period spanned the time from operation to discharge from the hospital.

2.4. Methods

2.4.1. McSPI Stroke Risk Index

The McSPI Stroke Risk Index consists of a logistic regression model based on seven risk factors:

- McSPI Stroke Risk Index \(= -8.8203 + 0.0619 \cdot \text{age in years} + 0.5835 \cdot \text{unstable angina} + 0.8244 \cdot \text{history of neurologic disease} + 0.6378 \cdot \text{prior CABG} + 0.7390 \cdot \text{history of vascular disease} + 0.7421 \cdot \text{diabetes} + 0.6312 \cdot \text{history of pulmonary disease} \)

Fig. 1. EMBOL-X® Intraaortic Filtration System showing filter cartridge inserted in cannula and filter mesh deployed.

Fig. 2. Gross visual examination at 10× magnification of particulate found in filter mesh (grid = 3mm) from 67-year-old male presenting with myocardial infarction more than 7 days preoperatively, ventricular arrhythmia, obesity, transient ischemic attack, renal dysfunction, hypertension and hypercholesterolemia. Operative history was elective CABG using aortic and partial cross clamps. Aortic assessment was friable, no calcification. Total bypass time was 51 min; filter dwell time was 30 min.
Except for age, all risk factors were dichotomous, and coded as 1 for ‘yes’ and 0 for ‘no.’ To illustrate, a 68-year-old patient with chronic stable angina (unstable angina = 0), with a history of a prior stroke (history of neurologic disease = 1) and peripheral vascular disease (history of vascular disease = 1), but non-diabetic (diabetes = 0) and having no history of pulmonary disease (history of pulmonary disease = 0), would have a Stroke Risk Index of 

\[ P = 1/[1 + \exp(-\text{Stroke Risk Index})] \]

where \( \exp \) is \( e \), the base for the natural logarithms.

Thus, the example patient would have a predicted probability of experiencing a perioperative neurologic event of 4.5%.

These equations were solved for each patient in the study database. The individual probabilities were then summed to yield the expected number of events for the group.

To apply accurately the McSPI Stroke Risk Index, the variables used in developing the index must correspond in definition and coding to variables in the ICEM data set. The correspondence between ICEM variables and McSPI Stroke Risk Index variables is outlined in Table 1. Two factors, unstable angina and history of neurologic disease, were not directly recorded in ICEM data, but closely matching surrogates were used. Patients presenting as either class III or class IV on the New York Heart Association (NYHA) scale were categorized as positive for unstable angina. In addition, only patients with either previous stroke or TIA were categorized as positive for history of neurologic disease.

### 2.5. Missing values

Although 114 variables were collected on each ICEM patient, this comparison focused only on the seven variables relevant to the McSPI Stroke Risk Index. Dataset completion of all variables was very high, ranging from 94% (NYHA class, surrogate for unstable angina) to 100% (prior CABG). Because missing data from patient records was sporadic, mean values for the group from whom the data was available were substituted in order to apply the McSPI Stroke Risk Index appropriately. However, any patient missing age or more than two values for variables was excluded.

### 2.6. Comparison of observed and predicted events

Observed and predicted events were assessed in terms of their 95% confidence intervals, and were compared using a chi-square goodness-of-fit test.

### 3. Results

#### 3.1. McSPI Stroke Risk Index variables

Occurrence of patient risk factors are summarized and compared to those of Newman and colleague’s McSPI patient population in Table 2. The mean age of ICEM patients was slightly higher than that of the McSPI patients. Preoperatively, ICEM patients exhibited more unstable angina and vascular disease, but less diabetes, neurologic disease, prior CABG, and pulmonary disease, when compared to McSPI patients. As a whole, the ICEM and McSPI patient subsets were reasonably matched, with neither group being uniformly higher risk across risk factors.

<table>
<thead>
<tr>
<th>Patient risk factors</th>
<th>ICEM</th>
<th>ICEM n</th>
<th>McSPI</th>
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<tbody>
<tr>
<td>Unstable angina</td>
<td>67%</td>
<td>252/378</td>
<td>47%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>21%</td>
<td>83/398</td>
<td>26%</td>
</tr>
<tr>
<td>History of neurologic disease</td>
<td>9%</td>
<td>34/400</td>
<td>14%</td>
</tr>
<tr>
<td>Prior coronary artery bypass graft</td>
<td>5%</td>
<td>20/402</td>
<td>13%</td>
</tr>
<tr>
<td>History of vascular disease</td>
<td>26%</td>
<td>103/402</td>
<td>21%</td>
</tr>
<tr>
<td>History of pulmonary disease</td>
<td>14%</td>
<td>56/395</td>
<td>18%</td>
</tr>
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</table>

### Table 2

International Council of Emboli Management (ICEM) patient risk factors compared to Newman’s Multicenter Study of Perioperative Ischemia (McSPI) findings.

<table>
<thead>
<tr>
<th>Patient risk factors</th>
<th>Mean</th>
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<tr>
<td>Age (years)</td>
<td>67</td>
<td>65</td>
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</table>
3.2. Observed neurologic events

Five patients suffered a stroke (1%) and one patient suffered a TIA (0.2%). One of the stroke patients suffered a prolonged coma (0.2%). In all, six patients had outcomes consistent with the McSPI criteria for adverse perioperative neurologic outcomes, 1.5% (95% confidence limits 0.6–3.4%).

3.3. Comparison of observed and predicted events

Application of the McSPI model resulted in probabilities of neurologic events ranging from 0.16–42.9%. Calculated expected number of adverse neurologic outcomes was 13.7, 3.4% (95% confidence limits 2.0–5.8%). This difference was unlikely to be due to chance, \( P = 0.03 \).

4. Discussion

Adverse neurologic outcomes remain one of the most intractable problems in cardiac surgery [6]. Recent studies have shown that despite surgical improvements and modifications, the occurrence of severe and clinically evident neurologic complications stubbornly hovers between 1.4–3.4%. These rare events result in a sixfold increase in hospital mortality, hospital length of stays over 25 days, and dramatically increased hospital costs [7–10].

Attempts to study the possible benefits of devices proposed to reduce clinically evident neurologic events have been thwarted by their relatively rare occurrence, resulting in sample sizes for possible clinical trials of many thousands of patients [11]. Further, the multifactorial origin and methodological complexity of studying neurologic injury, defined by neurologic signs and symptoms, or neurocognitive deficits, or other neurobiology markers in the cardiac surgical setting, make a randomized trial very large, expensive, and difficult to sustain. Thus, in the present study, the application of an independently derived, validated regression model explicitly developed to predict neurologic outcomes and compare predicted to observed outcomes, provided an alternative for understanding non-randomized, but prospective, data.

4.1. McSPI Stroke Risk Index

While several studies have described predictive risk factors for adverse neurologic events, the McSPI Stroke Risk Index was selected for comparison in this ICEM study because it was based on a comparable patient population and was a large randomized sample of prospective data with preoperative variables [12–14]. The strength of the McSPI Stroke Risk Index is derived from data on 2017 patients from 24 different centers in the United States. The size of the database combined with the breadth of centers ensures that the resulting formula avoids the pitfalls of smaller, single-institution studies. In addition, the McSPI Stroke Risk Index has been validated as a multivariable predictive model of adverse perioperative neurologic outcomes while other studies have been limited to defining predictive risk factors for neurologic events [15–18].

Similarly, the ICEM database was prospectively collected from 15 diverse European centers, thereby yielding a multicenter cross section of patients and minimizing potential bias from individual surgeons or centers. In addition, both studies concentrated on preoperative, intraoperative, and postoperative variables specifically associated with neurologic injury versus evaluation of risk of overall cardiac surgery complications.

4.2. Principal finding

The occurrence of neurologic events in patients who had intraaortic filtration was low. Observed events were roughly half the number predicted, consistent with previous suggestions that Type I neurologic events are unusually low in a high-risk population of patients whose cardiac surgery was accompanied by intraaortic filtration. Harringer and coinvestigators reported 1.4% Type I events (stroke, coma, TIA, and death due to neurologic causes) in a dataset of patients that included valve and combination valve and CABG procedures [4]. In that dataset of patients, a higher proportion of preoperative risk factors compared to the Roach study were also noted.

4.3. Limitations

Limitations of this study include the confounding factors inherent in any cross-study comparison, such as differences in time and place: McSPI data were collected in the United States from 1991 to 1993; ICEM data were collected in Europe from 1999–2000. The ICEM data were self-reported, and in neither ICEM nor McSPI did patients undergo a preoperative and postoperative neurologic examination by a neurologist. In McSPI, a panel of experts adjudicated the appropriate neurologic outcome categorization. In this ICEM study, neurologic outcomes were identified by each center, and there may be varying sensitivity to the detection of adverse outcomes between centers. Every effort was made to compare the ICEM and McSPI preoperative variables consistently, nevertheless, some difference between the study populations is inherent. Slight differences in data formats meant that proxies were established for some risk factors. The use of NYHA angina class as a proxy for unstable angina may have overestimated this risk factor in the ICEM study group. Because only patients with a prior stroke or TIA were considered to have a history of neurologic disease, this risk factor may have been underestimated in the ICEM study population. Finally, the recent introduction of intraaortic filtration means that the study population of CABG patients is still relatively small.
5. Conclusion

This study demonstrates the use of a validated McSPI Stroke Risk Index to interpret the meaning of a low occurrence of adverse neurologic injury events among patients enrolled in a prospective multicenter non-randomized registry of patients undergoing cardiac surgery with conventional cardiopulmonary bypass using an intraaortic filter. In this study, patients undergoing CABG with intraaortic filtration experienced half the expected number of adverse neurologic events. These data suggest that intraaortic filtration of particulate matter may reduce neurologic damage from cardiac surgery.

References


Appendix A. International Council of Emboli Management Study Group

<table>
<thead>
<tr>
<th>Center</th>
<th>Principal investigator</th>
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<tbody>
<tr>
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<td>Professor Torkel Åberg</td>
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<td>University of Innsbruck</td>
<td>Dr Johannes Bonatti</td>
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<tr>
<td>St. Antonius Ziekenhuis</td>
<td>Dr Wim Jan van Boven</td>
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<td>Huddinge University Hospital</td>
<td>Dr Jan van der Linden</td>
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<tr>
<td>University of Vienna</td>
<td>Professor Michael Grimm</td>
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<tr>
<td>Hannover Medical School</td>
<td>PD Dr Wolfgang Harringer</td>
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<tr>
<td>Santa Cruz Hospital</td>
<td>Professor Joao Queiroz E. Melo</td>
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<td>J.W. Goethe University Frankfurt</td>
<td>PD Dr Gerhard Wimmer-Greinecker</td>
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Appendix B. Conference discussion

Dr V. Subramanian (New York, NY, USA): This is an excellent paper, once again trying to advance prevention of stroke after coronary bypass surgery. Our own group and the group of Dr Kronzon from NYU has shown the most important predictive factor in postoperative stroke after cardiac surgery is Grade IV or Grade III atheroma detected by transesophageal echocardiography (TEE). How many patients in this group have had TEE
to define the atheroma grade, and have you found any correlation between that and the capture of atheroma in the filter?

In patients with bad aortic atheroma, stroke is not the only end-organ failure one observes. Most often one sees some rise in creatinine and renal dysfunction. Have you any information on the postoperative renal function even though you prevented stroke in this group of patients? I enjoyed your paper.

Dr Schmitz: Thank you very much for these questions. First, these data are the cumulative results from 15 centers, several of which are routinely performing epiaortic scanning and transesophageal echo. Approximately 40% of the patients are being imaged and we are particularly interested in the potential relationship between advanced aortic disease and the presence of atheromatous material in the filter. To date, we have not seen a relationship, but this may be due to the small number of patients on whom data is available.

As to the second question, in this paper we have looked primarily at major perioperative neurologic events. Although data has been collected on other clinical complications, we have not yet analyzed the data.

Dr T. Lajos (Buffalo, NY, USA): I have a suggestion; it would be worthwhile to break down your group of patients to primary and reoperative group. We all know that with reoperative patients we have a higher incidence of adverse neurological complications, so it would bring out more the statistical differences.

The second point I would like to make is to avoid the pump and the partial clamping like in OPCAB. If this is omitted and one does not manipulate the aorta at all, doing the bypasses off-pump, through a left thoracotomy, LAST operations (MIDCAB) or gastroepiploic bypass; there will be a very low incidence of thromboemboli.

Dr Schmitz: I agree with you totally. I think that omitting bypass is the best way of decreasing the incidence of some complications, but there will still be a certain number of patients who will require cardiopulmonary bypass. For these patients, the EMBOL-X intraaortic filter may be helpful. In previous studies we have been able to show a statistically significant relationship between the repositioning of the partial clamp and the capture of atheromatous debris. This may be particularly important in many OPCAB procedures that also utilize a partial clamp for proximal anastomoses. Previous reports from the study group have demonstrated the presence of atheromatous emboli retrieved by an intraaortic filter in beating heart procedures. With regards to your first question, I agree that it would be very interesting to have a look at redos. But major neurologic complications are still relatively rare, and if we break down our study population into redos vs. primary cases, the number in each group becomes very small. We will need quite a lot of patients to find statistically significant differences given that complications are relatively rare. We expect to continue to gather data on specific subgroups so that these analyses can be made in the future.

Mr S. Large (Cambridge, UK): I enjoyed your paper very much indeed. I would like to just take you back to work done quite a few years ago in the UK by Pam Shaw. The reason for doing that is to question you on the definition of stroke and the definition of transient ischemic episode, because there is a huge room for error here. Of course if you remember Pam Shaw’s work, we saw something like 60% of patients within the first week to have demonstrated focal neurological lesions, but once reassessed three months later, only 2% were troubled by persisting signs. So can you share with us your definition of stroke and a definition of timing of assessment of stroke?

Dr Schmitz: At our center we are currently performing an extensive neurologic and neurocognitive test battery on all of our patients, including the NIH stroke scale. In this study, we have focused on major perioperative neurologic events only. We used a clinical definition of stroke, in which patients had a major event as determined by neurologist’s assessment and CT or MRI scanning and who had continued significant stroke at the time of discharge. At our center, we follow these patients on a daily basis during the first week, and perform a follow-up battery of tests at baseline, 48 hours, and 2 months postoperatively.

Dr R. Griepp (New York, NY, USA): Cerebral atheroembolism is certainly an important problem in North America as well as here in Europe. As one who has looked inside a number of aortas, I have seen how common it is to have mobile or semimobile atheroma in the portion of the aorta we manipulate so frequently in cardiac surgery. This study nicely points out that looking at strokes alone undoubtedly underestimates by a great deal the number of patients who sustain cerebral atheroemboli. I have a personal prejudice that pump brain is not a mysterious entity, but represents brains that have a large number of microscopic atheroemboli showered into them during the conduct of an operative procedure. Clearly this is one of the major problems in cardiac surgery in our present patient population.

I think there are other ways of approaching this problem, however, I suspect that if you cannulate the ascending aorta in a patient who has atheroma in the ascending aorta or the arch that the simple act of putting in the cannula or some sort of filter will dislodge some of this material. Auxiliary artery cannulation avoids manipulation of the aorta and in general provides inflow through vessels that are not themselves likely to have loose plaque within them. Although we started using auxiliary cannulation for ascending aortic and arch reconstructions, we believe that in addition it has reduced the incidence of embolic stroke in elderly patients having coronary bypass and aortic valve replacement as well.

Many of us also feel that the technique of doing all the coronary bypass procedures on single aortic cross-clamping is also likely to reduce the incidence of atheroembolization. One additional technique that we feel is useful is to leave the sutures on the proximal anastomoses between the vein grafts and the proximal aorta open until the cross-clamp is removed and allow a liter or two of blood to flush back from the clamp site through the open proximal anastomotic sites before pulling up and tying the sutures. On a number of occasions we have seen small bits of atheroma undoubtedly loosened by placing the aortic cross-clamp flush out on the proximal anastomotic sites after the clamp is removed.

Dr Schmitz: Thank you very much for this interesting comment. Although we presented one way to reduce neurologic complications, I think there are many ways of dealing with the problem. It may be that there is not one solution but that the combination of surgical management, intraaortic filtration and the use of beating heart procedures will help us eventually eliminate one of the worst complications confronting surgeons today.