The Impact of Microemboli During Cardiopulmonary Bypass on Neuropsychological Functioning

W. Pugsley, FRCS; L. Klinger, MSc; C. Paschalis, MD; T. Treasure, FRCS; M. Harrison, FRCP; S. Newman, DPhil

Background and Purpose Microemboli have been implicated in the etiology of neuropsychological deficits after cardiopulmonary bypass. This study examined the incidence of high-intensity transcranial signals (microemboli) and their relation to changes in neuropsychological performance after surgery.

Methods Transcranial Doppler ultrasonography was used to measure middle cerebral artery blood flow velocity and detect microemboli. The number of high-intensity transcranial signals was determined and related to a neurological examination and absolute changes in neuropsychological performance as well as the number of patients considered to exhibit a neuropsychological deficit. Data were available on 100 consenting patients undergoing routine cardiopulmonary bypass. Fifty of the patients were randomly assigned to a procedure that included a 40-μm arterial line filter, and 50 had the procedure without any arterial line filter.

Neuropsychological tests sensitive to quite subtle changes in intellectual function have detected impaired cerebral function in up to a third of patients after coronary artery surgery.1-3 The etiology of this cerebral injury is multifactorial, but microemboli have been implicated.4,4 That microemboli, gaseous and particulate, occur during cardiopulmonary bypass (CPB) is beyond question, but how damaging they are is a matter of considerable debate.4,7

In 1974 Aberg and Khilgren8 published their work on the effect of open heart surgery on intellectual function. In this early study on the neuropsychological outcome of cardiac surgery, only 6 patients of 144 studied had a microcure filter in the arterial line. On the basis of their performance on a battery of six tests administered preoperatively, 8 days after surgery, and again 8 weeks after surgery, Aberg and Khilgren concluded that arterial line filters confer a degree of protection against cerebral injury during CPB.8

On theoretical grounds arterial line filters might prevent cerebral damage by removing microemboli from the circulation. In dogs a rise in cerebrospinal fluid brain creatine phosphokinase can be demonstrated during CPB.9 This rise is almost entirely eliminated when arterial line filters are used, suggesting a marked reduction in brain cell damage. Wilner et al10 studied the effect of different arterial line filters on neuropsychological outcome, using the Conceptual Levels Analogy Test. They were able to show greater cerebral protection with one particular type of filter but did not control the study by including a nonfiltered group. Garvey et al11 using the Conceptual Levels Analogy Test, compared 56 patients operated on in 1972 without arterial line filters with 46 patients operated on with two different types of arterial line filters in 1981, a full 9 years later. They were unable to show a significant difference in postoperative performance between the three groups.

Aris et al12 using a battery of seven psychometric tests on 100 patients randomized to filtered or nonfiltered CPB, were unable to demonstrate any cerebral protective effect from a 20-μm nylon screen filter placed in the arterial line.

The picture is further clouded by evidence that filters themselves may generate emboli downstream of the filtering element.13 It is thus conceivable that they may add to the cerebral impairment observed after CPB. Our own transcranial Doppler studies14 showed a very marked reduction in high-intensity transcranial signals (HITS) (microemboli) reaching the brain during CPB when a 40-μm screen filter is placed in the arterial line. We now present the results of the neuropsychological evaluation of the patients randomized to filtered and nonfiltered CPB in our study.
Subjects and Methods

One hundred five patients who underwent elective coronary artery surgery at the Middlesex Hospital were randomized into two groups. This project was approved by the local ethics committee, and all patients gave informed consent. In group 1 a 40-μm absolute screen filter (Pall, EC Plus) was placed in the arterial line of the CPB circuit. In group 2 no arterial line filter was used. Patients aged older than 70 years were excluded, as were those with a history of transient ischemic attacks or stroke and those with metabolic disturbance such as diabetes or uremia. The statistical technique of interrupting randomization for minimization was used to ensure that the groups were compatible in terms of age, sex, and length of bypass (determined preoperatively by the number of grafts to be performed). Anesthetic technique was standardized, and prebypass PacO₂ was carefully monitored and controlled to eliminate any differences between the groups (Table 1).

Surgical technique was standardized, as was the maintenance of CPB. Harvey (H-1700) elliptical model bubble oxygenators were used in conjunction with Stockard “multiflow” roller pumps in pulsatile mode and polyvinyl chloride tubing. The oxygenator was primed with 1.5 L of Hartman’s solution, and bypass was instituted at a flow of 2.4 L/m² of body surface area at 37°C, reducing to 1.8 L/m² at 28°C. Perfusion pressures were regulated pharmacologically to maintain a mean pressure between 60 and 100 mm Hg. Phenylephrine was used to increase pressure, and phentolamine was used to reduce it; these drugs were chosen because they do not independently influence cerebral blood flow.15,16

CPB was instigated between an arterial line and right atrial basket; cold hyperkalemic (cardioplegia) solution was used for myocardial protection.

Monitoring

Blood pressure was recorded from an indwelling radial arterial line, and nasopharyngeal temperature was measured. Pump flows were monitored. Cerebral function was monitored by a cerebral function analyzing monitor. Transcranial Doppler (TC2-64, EME) was used to record middle cerebral artery blood flow on one side and to detect HITS. Counts of HITS were performed by means of a program on an Apple Ile microcomputer, which assessed the record for high-amplitude spikes (Fig 1). These were set at a point exceeding any recorded blood pressure peak. The probe was maintained in position manually using auditory feedback to ensure correct positioning. Recordings were carried out from the time the chest was opened until the discontinuation of bypass. All these variables were recorded and stored by Apple Ile microcomputers as previously described.14 By careful attention to monitoring it was possible to ensure that there were no gross hemodynamic intraoperative differences between the two groups of patients. Any deviations from the stipulated limits were immediately corrected, and any protocol violation resulted in elimination of that patient from the study.

Patient Assessment

Neurological Examination

A formalized version of the standard clinical neurological examination was performed by a neurologist who was “blind” to the randomization. Each patient was examined preoperatively, on the first postoperative day, 8 days after surgery, and again when the patient underwent outpatient review 8 weeks after surgery. On the first postoperative day particular attention was given to the identification of “soft” signs, namely, drowsiness, incoordination, nystagmus, and depressed reflexes. At all examinations cranial nerve function, with the
exception of smell and taste, was tested, and particular attention was given to identifying visual field defects.

Neuropsychological Examination

The neuropsychological examination used was developed at the Middlesex Hospital Medical School in 1985 and has been previously reported. It includes a battery of 10 carefully selected tests designed to test the patient’s memory, visual motor skills, reaction time, and attention. The tests are as follows:

**Test 1. Letter Cancellation Test:** This test consists of a matrix of 900 letters (30 rows and 30 columns) from which the subject is required to delete all the instances of the letter “p.” The time to complete the form and the number of errors (omission and commission) are scored. This test has been used for studies investigating the effects of anesthesia, and similar tests have been applied to Korsakoff and Parkinson patients.19

**Test 2. Trail Making Test Part A.**

**Test 3. Trail Making Test Part B.**

**Test 4. Computerized Symbol Digit Replacement Test:** This test is based on Smith’s (1968) Symbol Digit Replacement Test and involves three parallel versions, all of which are performed on a microcomputer.21

**Test 5. A computerized two-choice reaction time task. Subjects were required to respond selectively to two letters displayed on the computer screen.**

**Test 6. Purdue Pegboard Test.**

**Test 7. Rey Auditory Verbal Learning Test.**

**Tests 8 and 9. Two computerized nonverbal recognition memory tests.**

**Test 10. Block design subtest of the Wechsler Adult Intelligence Scale (WAIS-R).**24 Estimates of verbal intellectual abilities were obtained by administering the Vocabulary subtest of the WAIS-R, and those of nonverbal intelligence were obtained by means of the Picture Completion subtests of the WAIS-R. These tests were only performed before surgery.

The neuropsychological assessments were performed blinded to the randomization.

Definitions

In this study both deterioration and deficit in postoperative neuropsychological performance were examined, and differences between the two groups were studied.

Deterioration is defined as any drop in postoperative score compared with the preoperative score achieved by that patient, however small the difference and even if the drop occurs on only one test.

The definition of neuropsychological deficits in the field of cardiac surgery has been the subject of much discussion. We have previously defined a neuropsychological deficit, and this definition was applied in this study. An SD unit for each test is computed from all the preoperative scores. A deficit occurs in a test when the patient’s postoperative score has dropped by 1 SD unit or greater from the preoperative score. For the deficit to be significant it must occur in two more tests. Multiple scores on a single test are not considered as independent deficits for the purposes of the assessment of an overall neuropsychological deficit. This conventional definition has been widely applied in research on neuropsychological changes after cardiac surgery.

Statistical Analysis

Performance trends by the two groups across the whole battery of 10 tests were studied by binomial distribution. Intergroup comparisons of proportions of patients with deterioration or deficit were performed by the χ2 test. Comparisons of performance of the groups on any one test were determined by the Mann-Whitney U test.

### Results

One patient died within 8 days of surgery and did not complete the postoperative evaluation. Four patients were excluded because of protocol violations: 3 because drugs not specified in the protocol were given and 1 because the perfusion pressure limits were not adhered to, and this was reflected in the patient’s computerized records. One hundred patients (50 from each group) were therefore available to complete the study.

Neurological Studies

No patient in either group had focal neurological signs 24 hours, 8 days, or 8 weeks after surgery. There was a significantly higher incidence of soft neurological deficit in the nonfiltered group 24 hours after surgery (Table 2). No focal neurological signs were found in either group at 24 hours, 8 days, or 8 weeks after surgery.

Neuropsychological Assessment

Preoperative Assessment

The preoperative assessments of IQ based on the revised WAIS (WAIS-R) indicated that the two groups were of average intelligence, and no differences were found between the groups on IQ estimates or any of the subtests. There was also no significant difference between the two groups in preoperative performance of any of the other tests.

Eight Days After Surgery

Complete neuropsychological results from the battery of 10 tests were available for 26 of 50 filtered patients and 31 of 50 nonfiltered patients. Three patients in group 1 and 5 in group 2 were unable to complete the battery of tests because of exhaustion. The remaining

<table>
<thead>
<tr>
<th>TABLE 2. Neurological Examination: Soft Neurological Signs in Filtered and Nonfiltered Patients</th>
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<tr>
<td>Filtered CPB</td>
</tr>
<tr>
<td>Normal neurology</td>
</tr>
<tr>
<td>Soft signs</td>
</tr>
</tbody>
</table>

CPB indicates cardiopulmonary bypass. *P<.05 (χ2).

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FIG 2. Bar graph shows neuropsychological deterioration at 8 days in filtered (F) and nonfiltered (NF) patients. NA and NB are the two nonverbal memory tests; Bio, the Block Design Subtest of the Wechsler Adult Intelligence Scale, Revised; TA and TB, the Trail Making Tests A and B; CT, the Choice Reaction Time Test; LX, the Letter Cancellation Test; SR, the Symbol Digit Replacement Test; PR, PL, and PB are limbs of the Purdue Pegboard Test; and RA, RB, RC, RD, RE, RF, and RG are trials of the Rey Auditory Verbal Learning Test.
patients (21 from group 1 and 14 from group 2) were discharged from the hospital before the eighth day. When this happened the patients were tested on the fifth or sixth postoperative day. We did not feel that results of these earlier tests should be included for comparison with 8-day test results, but we did ensure that the patients all encountered the tests on three occasions so that any opportunity for learning would be equal for all patients. In general patients tested at 5 or 6 days after surgery struggled to complete the tasks. No patients were on sedatives at 8 days.

**Deterioration in Performance.** On the 8-day assessment 96.5% of patients showed some degree of deterioration in performance on the tests. In the filtered group 24 of 26 patients showed deterioration; 31 of 31 of the nonfiltered group had deteriorated. Fig 2 shows how this deterioration is distributed across the tests. Each limb of the Purdue Pegboard Test (PR, PL, and PB) is shown separately, as is each trial of the Rey Auditory Verbal Learning Test (RA, RB, RC, RD, RE, RF, and RG). It is clear that within each trial of each test, the filtered patients showed less deterioration than the nonfiltered patients ($P<.05$, binomial).

**Neuropsychological Deficit.** A deficit in performance occurred in 12 of 26 filtered patients and 22 of 31 nonfiltered patients (Table 3) on the 8-day assessment ($P<.05$, $\chi^2$).

**Eight Weeks After Surgery.**

Complete neuropsychological results from the battery of 10 tests was available for 49 of 50 filtered patients and 45 of 50 nonfiltered patients. One group 1 patient failed to complete the tests at 8 weeks. One group 2 patient had exhibited maturity-onset diabetes in the postoperative period and had started on insulin, and she refused the 8-week assessment. One patient declined the 8-week assessment because he had no time, and 3 patients were unable to complete the tests because of fatigue or disinterest.

**Deterioration in Performance.** On the 8-week assessment 94.6% of patients showed some degree of deterioration in performance on the tests. In the filtered group 45 of 49 patients showed deterioration, and 44 of 45 of the nonfiltered group performed less well than preoperatively. Fig 3 shows how this deterioration is distributed throughout the tests. Again each limb of the Purdue Pegboard Test (PR, PL, and PB) is shown separately, as is each trial of the Rey Auditory Verbal Learning Test (RA, RB, RC, RD, RE, RF, and RG).

Within each trial of each test, the filtered patients showed less deterioration than the nonfiltered patients except in Trailmaking Test B, where there was no significant difference in performance between the groups, and in the Purdue Pegboard Test, where the nonfiltered patients actually showed less deterioration. That the filtered patients showed less deterioration on 8 of 10 tests is significant ($P<.05$, binomial).

**Neuropsychological Deficit.** A deficit in performance occurred in 4 of 49 filtered patients and 12 of 45 nonfiltered patients (Table 4) at the 8-week assessment ($P<.03$, $\chi^2$).

**Verbal Memory: Rey Auditory Verbal Learning Test.**

From Fig 3 it is clear that the greatest difference between the two groups is seen in the Rey test. We have therefore examined this test in detail, looking at each limb separately. Fig 4 shows the result of the second reading of the Rey (RB) in 49 filtered and 48 nonfiltered patients. The patients' preoperative scores were subtracted from scores 8 weeks after surgery. No change in performance is shown along the zero line. Scores above zero indicate improved performance, and negative scores indicate a deterioration in performance. In the

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**Table 3. Neuropsychological Deficit at 8 Days in Filtered and Nonfiltered Patients**

<table>
<thead>
<tr>
<th>No. of Tests Showing Deficit</th>
<th>Filtered</th>
<th>Nonfiltered</th>
</tr>
</thead>
<tbody>
<tr>
<td>No deficit</td>
<td>0-1</td>
<td>14</td>
</tr>
<tr>
<td>Deficit</td>
<td>&gt;1</td>
<td>12</td>
</tr>
</tbody>
</table>

$\chi^2=3.62$. 

**Table 4. Neuropsychological Deficit at 8 Weeks in Filtered and Nonfiltered Patients**

<table>
<thead>
<tr>
<th>No. of Tests Showing Deficit</th>
<th>Filtered</th>
<th>Nonfiltered</th>
</tr>
</thead>
<tbody>
<tr>
<td>No deficit</td>
<td>0-1</td>
<td>45</td>
</tr>
<tr>
<td>Deficit</td>
<td>&gt;1</td>
<td>4</td>
</tr>
</tbody>
</table>

$\chi^2=5.69$. 

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Fig. 3. Bar graph shows neuropsychological deterioration each test at 8 weeks in filtered (F) and nonfiltered (NF) patients. NA and NB are the two nonverbal memory tests; Bio, the Block Design Subtest of the Wechsler Adult Intelligence Scale, vised; TA and TB, the Trail Making Tests A and B; CT, the Continuous Reaction Time Test; LX, the Letter Cancellation Test; SR, the Symbol Digit Replacement Test; PR, PL, and PB are limbs of the Purdue Pegboard Test; and RA, RB, RC, RD, RE, RF, and RG are trials of the Rey Auditory Verbal Learning Test.

Fig. 4. Plot shows verbal memory score change at 8 weeks in filtered (F) and nonfiltered (NF) patients on second reading of the Rey Auditory Verbal Learning Test (REYB).
majority of cases performance was improved or at least unaltered. As a group the nonfiltered patients performed less well than their filtered counterparts, showing that the nonfiltered patients had a higher incidence of memory impairment ($P=0.007$, Mann-Whitney).

To illustrate the differences between the groups, each of the limbs of the Rey test were examined in this way. The results for the fifth (RE) and seventh (RG) trials are shown in Figs 5 and 6, respectively. Although it is important to recognize that these trials are not independent of each other, it is striking that on each trial the filtered patients performed significantly better than the nonfiltered patients (Table 5).

Relations Between Microemboli Count and Neuropsychological Deficit

We previously presented the results of transcranial Doppler detection of HITS during CPB.\(^1\)\(^4\) In this study all 94 patients who completed the neuropsychological assessment at 8 weeks had successful transcranial Doppler recordings. Using these data, we were able to examine the neuropsychological deficit encountered in 16 patients (4 filtered and 12 nonfiltered), with the HITS count expressed as a total for the whole of the patient's bypass time. When the HITS count was less than 200, only 5 of 58 patients (8.6%) exhibited a deficit at 8 weeks. When the count was greater than 1000, 3 of 7 patients (43%) were found to have a deficit in postoperative neuropsychological performance (Table 6). Pulsatility of flow was found to be reduced during CPB. Although the paradigm used for the detection of emboli did not store velocity data, it was apparent on

subjective examination that this phenomenon was similar in both the filtered and nonfiltered groups.

Discussion

We previously reported our findings that a 40-μm filter placed in the arterial line reduced the incidence of microemboli in the middle cerebral artery to virtually zero.\(^1\)\(^4\) The present study also shows a reduction in neuropsychological impairment associated with coronary artery surgery when an arterial line filter is placed in the bypass circuit, both in terms of the number of patients affected and the extent of deterioration. Other investigators have not been able to show any clear-cut benefit from filters.\(^1\)\(^0\)\(^-\)\(^1\)\(^2\) We were careful to standardize anesthetic and surgical factors that might lead to cerebral injury. Our prospective randomized trial produced two groups with no age difference or significant difference in bypass times. The prebypass $\text{Paco}_2$ was carefully controlled, and perfusion variables were monitored and regulated. We are thus confident that the only major difference between the groups was the use of an arterial line filter in one group. The battery of neuropsychological tests used have had a wide exposure\(^2\) and have been used to assess the effects of circulatory arrest\(^2\) as well as coronary artery surgery and other major vascular and thoracic procedures. Eight days after surgery there was marked deterioration, and even deficit, in performance in the majority of patients; there was no major difference between filtered and nonfiltered groups. Performance on the tests at this early stage after surgery is undoubtedly influenced by postoperative factors such as tiredness, pain, analgesic effects, hypoxia, and pulmonary atelectasis. The specific effect of any operative

![Fig 5. Plot shows verbal memory score change at 8 weeks in filtered (F.) and nonfiltered (NF.) patients on fifth reading of the Rey Auditory Verbal Learning Test (REYE).](http://stroke.ahajournals.org/)

![Fig 6. Plot shows verbal memory score change at 8 weeks in filtered (F.) and nonfiltered (NF.) patients on seventh reading of the Rey Auditory Verbal Learning Test (REYG).](http://stroke.ahajournals.org/)
intervention might thus be masked. Aris et al.\(^2\) were unable to show any significant difference in performance on seven psychometric tests applied to two groups 10 days after surgery with or without a 25-μm nylon screen filter. The incidence of deficit by his criteria was high (61%), and we must suspect that the tests were performed too early after surgery for any difference due to the filters to be apparent.

Alternatively, it may be the filter material that is wrong; nylon may not confer benefit. When comparing studies on neuropsychological outcome after open heart surgery we must accept that there is great disparity between the methods used by different groups such that the reported incidence of neuropsychological deficit varies from 0% to 90%.\(^2\) Our group has been consistent in finding deficits in approximately two thirds of the patients at 8 days and in one third at 8 weeks. We previously suggested that the presence of soft neurological signs 24 hours after surgery might predict neuropsychological deficit.\(^1\) This study confirms our initial impression; the higher incidence of soft signs in the nonfiltered group is commensurate with the subsequent neuropsychological outcome.

Eight weeks after surgery there was a marked difference between the two groups. The filtered patients showed less deterioration in performance overall; they performed better on 8 of 10 tests, and even when the rigorous definition of a deficit was applied, the filtered patients showed significantly less deficit in performance than the nonfiltered group. This latter finding is of major consequence; we had expected that the requirement of a 1 SD drop in performance on two or more tests would be too crude and revealing to ignore any benefit conferred by filters. The incidence of deficit in the nonfiltered group was 27%. This represents a slight but not significant reduction when compared with our earlier studies. It must be remembered that we excluded patients aged older than 70 years and were very attentive to the details of anesthetic technique and control of bypass, having taken into account lessons learned from earlier studies. The drop to a 9% incidence of deficit in the filtered group is significant and must be regarded as prima facie evidence of the benefit of filters.

The feasibility of detection of embolism by Doppler ultrasound was described initially in decompression sickness\(^26\) and fat embolism.\(^27\) Emboli have now been detected by transcranial Doppler in cardiac surgery,\(^28\) carotid endarterectomy,\(^29\) carotid thrombolysis,\(^28\) and in stroke-prone patients with atrial fibrillation or transient ischemic attacks.\(^31\) Although some work has suggested that the nature of emboli can be discriminated by transcranial Doppler signature,\(^32\) it is not yet possible to reliably distinguish bubbles from particulate matter in the context of a study such as ours.\(^4\) However, the fact that fewer emboli are detected when membrane oxygenators replace bubble oxygenators suggests that many are microemboli.\(^28\) The relation between the number of high-amplitude signals and particles in an in vitro validation model using the present transcranial Doppler equipment\(^6\) showed an effect of size that suggested that large emboli could give rise to more than one signal. The high-amplitude signal count is thus not a precise embolic count but a measure of embolic burden. For this reason we have referred to an HITS event rate.

We have shown that filters greatly reduce such events during CPB; the filters also protect against neuropsychological impairment. Finally, we are able to present evidence that a high HITS count is associated with a higher incidence of neuropsychological deficit. These data admittedly are based on only 16 patients who showed a deficit on the 8-week tests. Nevertheless, we should not ignore the 43% (confidence interval, 25% to 61%) incidence of deficit in the high (>1000) HITS count group compared with the 8.6% (confidence interval, 5% to 12.2%) incidence in the low (<200) HITS count group.

Conclusion
Microemboli as detected by HITS from the middle cerebral artery contribute to the neuropsychological deficits observed in routine CPB.

Acknowledgments
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