Transcranial Doppler Microembolus Detection in the Identification of Patients at High Risk of Perioperative Stroke*


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Objectives: Perioperative ischaemic stroke is the leading cause of morbidity and mortality associated with carotid endarterectomy (CEA). The aim was to test the hypotheses that the detection of microembolic ultrasonic signals (MES) with transcranial Doppler ultrasound (TCD) during and after the operation may be of value in identifying patients at increased perioperative stroke risk.

Design: Open prospective case series.

Patients and Methods: Eighty-one consecutive patients undergoing CEA with TCD monitoring. Preoperative, intraoperative and interval postoperative TCD monitoring of the middle cerebral artery (MCA) ipsilateral to the operated carotid artery. On-line pre- and intraoperative MES counting and blinded off-line analysis of postoperative MES counts. End-points were any focal neurological deficit and death at 30 days postoperatively.

Results: MES were detected in 94% of patients intraoperatively and 71% of cases during the first postoperative hour. MES counts ranged from 0 to 25 per operative phase (range of median counts 0-8) and from 0 to 212 per hour postoperatively (range of median counts 0-4). Eight cases (10%) developed postoperative MES counts greater than 50/h. Five of these eight cases evolved ischaemic neurological deficits in the territory of the insonated MCA, indicating a strong association between frequent postoperative microembolism and the development of early cerebral ischaemia ($\chi^2 = 34.2$, p<0.0001). Intraoperative MES were not associated with clinical outcome measures.

Conclusions: MES counts of greater than 50/h in the early postoperative phase of carotid endarterectomy are predictive of the development of ipsilateral focal cerebral ischaemia.

Key Words: Microemboli; Carotid endarterectomy; Perioperative stroke.

Introduction

Strategies capable of reducing perioperative morbidity and mortality in carotid endarterectomy (CEA) will increase the net benefit the procedure offers to patients with high grade symptomatic carotid artery stenosis.1,2 Such strategies may also improve the risk benefit ratio and cost-effectiveness of the operation in lower stroke risk situations such as asymptomatic carotid artery stenosis.3,4

Thromboembolic ischaemic stroke is the major complication of CEA, occurring most frequently in the first few hours postoperatively.5,6 Studies using transcranial Doppler ultrasound (TCD) to detect cerebral embolism during CEA have provided important insights into the pathogenesis of perioperative cerebral ischaemia.7-11 High risk periods for intraoperative brain embolism have been identified7,10 and associations noted between microembolic ultrasonic signal(s) (MES) during the operation and the development of both neuro-psychological impairment11 and asymptomatic ischaemic lesions on magnetic resonance (MR) brain imaging.9,12 Postoperative embolus detection monitoring has also identified cases in which frequent MES were associated with the development of ischaemic stroke.10-13 The value of TCD embolus detection in the identification of patients at risk of perioperative ischaemic neurological deficits, however, remains uncertain.

We hypothesised that the detection of intraoperative and postoperative MES may be of value in the identification of patients at risk of perioperative cerebral ischaemia, and that the frequency of MES may be an
important determinant in risk prediction. Based on published case reports\textsuperscript{10,11,13} and our own preliminary monitoring studies, we considered that MES counts of greater than 10 during any intraoperative phase and greater than 50/h at any postoperative phase were likely to be associated with the development of focal cerebral ischaemia.

To test these hypotheses we prospectively studied patients with intraoperative and postoperative TCD monitoring and clinical neurological assessments during the first 24 h following CEA. Clinical end-points were re-assessed at 30 days postoperatively.

**Patients & Methods**

Ninety consecutive patients who underwent CEA with TCD monitoring were studied from November 1993 to March 1996. Eighty-one cases (90\%) were successfully monitored postoperatively, and 74 cases (82\%) were successfully monitored both intraoperatively (at one or more stages) and postoperatively. Analyses of postoperative MES counts were performed on all 81 patients successfully monitored and analyses of intraoperative MES counts on the subset of 74 patients. In 15 patients Doppler signal quality was inadequate or monitoring failed. The breakdown of these patients was: eight with inadequate temporal ultrasonic windows, six in whom non-correctable probe dislodgement occurred, and one case of equipment failure. In the remaining case excluded from analysis, CEA was abandoned because the internal carotid artery (ICA) was found to be thrombosed at operation.

Patients enrolled in the study were screened for operative suitability by the Neurovascular Service, Austin & Repatriation Medical Centre, and the same six vascular surgeons performed all procedures. Digital subtraction angiography was used to delineate preoperative vascular anatomy in 74 cases, carotid duplex ultrasonography alone in four cases, duplex and MR angiography in one case and computed tomography (CT) angiography in two cases. Transient cerebral or retinal ischaemia preceded surgery in 54\% of cases, 18\% of patients had a preceding ischaemic stroke, and 28\% of cases were asymptomatic. Sixty-two per cent had 90–99\% ipsilateral carotid artery stenosis (North American symptomatic carotid endarterectomy trial measurement system\textsuperscript{14}). The demographic details of the patient group are shown in Table 1.

### Table 1. Characteristics of patient group (n = 81); mean age = 69 years (44–85); males n = 58; females n = 23.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Number (%)</th>
</tr>
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<tbody>
<tr>
<td>Clinical presentation</td>
<td></td>
</tr>
<tr>
<td>Transient cerebral or retinal ischaemia</td>
<td>44 (54)</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>14 (18)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>23 (28)</td>
</tr>
<tr>
<td>Angiographic stenosis</td>
<td></td>
</tr>
<tr>
<td>&lt;70%</td>
<td>4 (5)</td>
</tr>
<tr>
<td>70–79%</td>
<td>11 (15)</td>
</tr>
<tr>
<td>80–89%</td>
<td>14 (19)</td>
</tr>
<tr>
<td>90–99%</td>
<td>45 (61)</td>
</tr>
</tbody>
</table>

Preoperatively and postoperatively 30-minute monitoring sessions were performed. Seventeen cases underwent a single postoperative monitoring session commencing during the first postoperative hour, and 64 cases underwent serial postoperative monitoring sessions at the 0–1 h phase, 2–3 h phase, 4–6 h phase and at 24 h. Eighty patients underwent preoperative monitoring.

Two megahertz pulsed wave TCD systems (EME-Nicolet TC 2020, EME-Nicolet, Uberlingen, Germany or DWL MultiDop T, DWL Elektronische Systeme GmbH, Sipplingen, Germany) were used to insonate the middle cerebral artery (insonation depth 45–55 mm) ipsilateral to the operation side. An elasticised headband was used to fix the probe in position. The presence of the probe did not interfere with or necessitate modification of standard surgical technique or patient position. Instrument power output and gain settings were adjusted to provide an optimal signal to noise ratio and achieve a constant analog signal recording level. The Doppler signal was recorded continuously on digital audio tape (Sony TCD-D10 Pro II, Sony Corporation).

**TCD monitoring and data recording**

Intraoperative monitoring was continuous with online time linking of MES to specific operative phases.

**MES counting**

Preoperative and intraoperative MES counting was performed on-line by an experienced observer applying previously defined signal criteria.\textsuperscript{15} Postoperative MES counting was performed at blinded off-line review of the Doppler recordings (EME-Nicolet TC 2020; sweep speed 5.1 s). A 6 decibel (dB) intensity
Table 2. Operative phases, proportions of patients MES positive and median MES counts per phase.

<table>
<thead>
<tr>
<th>Operative phases</th>
<th>Mean time min (S.D.)</th>
<th>MES positive n (%)</th>
<th>Median (25%-75% quartile)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intraoperative</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. Preclamp dissection</td>
<td>26 (10)</td>
<td>26 (35)</td>
<td>0 (0-1)</td>
</tr>
<tr>
<td>B. Establishment of shunt flow</td>
<td>58 (94)</td>
<td>4 (2-6)</td>
<td></td>
</tr>
<tr>
<td>C. Endarterectomy phase and shunt flow established</td>
<td>39 (19)</td>
<td>16 (26)</td>
<td>0 (0-0.5)</td>
</tr>
<tr>
<td>D. Re-establishment of carotid flow</td>
<td>64 (86)</td>
<td>5.5 (2-8)</td>
<td></td>
</tr>
<tr>
<td>E. Wound closure</td>
<td>16 (6)</td>
<td>35 (49)</td>
<td>0 (0-3)</td>
</tr>
<tr>
<td><strong>Postoperative</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1 h postoperative (n=80)</td>
<td>57 (71)</td>
<td>4 (0-19)</td>
<td></td>
</tr>
<tr>
<td>2-3 h postoperative (n=60)</td>
<td>17 (28)</td>
<td>0 (0-2)</td>
<td></td>
</tr>
<tr>
<td>4-6 h postoperative (n=58)</td>
<td>14 (24)</td>
<td>0 (0-0)</td>
<td></td>
</tr>
<tr>
<td>24 h postoperative (n=56)</td>
<td>8 (14)</td>
<td>0 (0-0)</td>
<td></td>
</tr>
</tbody>
</table>

Threshold above peak background intensity was applied to on-line and off-line MES reporting. On-line intensities were estimated by visual assessment of the Doppler power/frequency spectrum displayed in 12 colours with 2 dB increments (128 point fast Fourier signal transformation). Background intensity was taken as the maximum intensity colour pixels in an equivalent region of the spectrum in the preceding or following cardiac cycle. MES intensities measured off-line were averaged from three spectral displays saved to hard disc from digital audio tape. Intensities above background were taken as the difference between the instrument calculated dB value for the maximum intensity pixels of the MES and the dB value of the maximum intensity pixels in an equivalent area of the background in preceding or following cardiac cycle. Differentiation between air and particulate embolism based on MES intensity measurements was not attempted during reporting.

Operative and treatment details

The intraoperative period was divided into phases, with mean time durations shown in Table 2. Sixty-eight cases underwent CEA performed through a longitudinal carotid arteriotomy (66 under general anaesthesia), and 13 cases underwent eversion CEA (10 under general anaesthesia). A common carotid to internal carotid artery shunt was inserted in 65 (96%) of conventional CEA cases and in two of the eversion endarterectomy cases. Patch angioplasty was performed in 26 cases (32%). Daily aspirin therapy was continued in all patients up to the day of surgery, and all cases received an intraoperative bolus dose of heparin. Protamine sulphate was given following arteriotomy closure in 39 cases (48%).

Clinical and radiological assessment

All patients underwent detailed preoperative neurological examination and serial postoperative neurological assessments at each TCD monitoring session. A further neurological assessment was performed at 30 days postoperatively. Clinical examinations were performed by a neurologist, with particular attention given to new signs of cortical dysfunction. The clinical outcomes assessed were death, new ischaemic stroke or witnessed transient ischaemic attack (TIA) within 30 days of surgery. Stroke handicap was assessed by modified Rankin scale and strokes classified as major (modified Ranking grade 3 to 5) or minor (modified Ranking grade 0 to 2).

In 62 cases, hard copies of intraoperative angiograms were available for review. Reporting was performed blind to other information, and the European carotid surgery trial stenosis measurement system was used to assess postoperative stenosis. A stenosis of greater than 30% diameter narrowing was considered a significant potential source of postoperative embolism.

Statistical methods

MES counts were not normally distributed, and are represented as ranges with median values and quartile

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rankings. MES counts at different operative phases were compared with preoperative baselines using the Mann–Whitney U test. To enable comparison of intraoperative embolism with the preoperative baseline, the preoperative counts were time-corrected for the mean duration of the preclamp dissection, endarterectomy with shunt and wound closure phases. Comparisons between groups for different outcomes were made using either the Chi-squared test or Fisher’s exact test. Significance was declared at \( p<0.05 \). Multivariate analysis was unable to be performed, as only a single patient had a cerebral ischaemic outcome event not associated with MES. Correlation between on-line and off-line MES reporting by a single observer during the first postoperative monitoring session was assessed using a Spearman rank correlation test. A proportion of agreement was calculated to assess the test/re-test agreement for MES reported at the same point in time by a single observer over 60 min of monitoring (observations separated by 2 weeks). Interobserver agreement for MES reported at the same point in time by three blinded independent observers was also assessed by calculating a proportion of agreement. The proportion of agreement defined the likelihood that a second and/or third observation will count a MES at the same point in time as a first observation. As observers were blind to the reports of their co-observers, time points at which all observers registered no MES could not be prospectively registered. This uncertainty precludes the use of Cohen’s kappa statistic for the assessment of inter-observer variation.

Results

Clinical outcome measurements and MES counts

At the 30-day assessment there was one major ischaemic stroke (modified Rankin grade 4) and three minor ischaemic strokes (modified Rankin grade 2) (overall stroke rate 5%, major stroke rate 1.25%). In addition, two episodes of transient ischaemia of less than 6 h duration occurred during the first 24 h postoperatively. All cerebral ischaemic events were ipsilateral to the operated carotid artery and were first documented within 3 h of the patient returning to the recovery room.

Following an initially normal neurological examination soon after the patient regained consciousness, TCD monitoring detected frequent MES in seven patients during the first postoperative hour and in one patient during the second postoperative hour. A strong association was evident between MES counts over 50/h at the 0–1 h phase and the development of clinical evidence of cerebral ischaemia \( (\chi^2 = 34.2, p<0.0001) \), as all three minor strokes and both episodes of transient ischaemia occurred following MES counts over 50/h during this period. Although patients were not formally examined whilst monitoring was in progress, neurological dysfunction appeared to develop gradually during the initial 30 min monitoring session. In the three patients with minor stroke, a further gradual worsening of neurological deficit was evident over 30 min to 1 h following completion of the first postoperative monitoring session. The positive predictive value for cerebral ischaemia of detecting postoperative MES counts over 50/h was 0.63, and negative predictive value for postoperative MES counts of less than 50/h was 0.98.

The one major stroke occurred in association with prolonged middle cerebral artery (MCA) signal loss after shunt insertion. The neurological deficit was evident immediately on the patient regaining consciousness following anaesthesia. There was one sudden cardiac death on day 2 postoperatively (death rate = 1.25%).

No patient with MES counts of greater than 10 during any intraoperative phase demonstrated signs of focal cerebral ischaemia on recovery from anaesthesia, and there was no significant association between intraoperative MES counts greater than 10 during any phase and clinical outcome measures at 30 days (Fisher’s exact, \( p=0.67 \)). Importantly, however, in only five of the 18 cases where intraoperative MES counts exceeded 10 during any operative phase could particulate embolism be confidently inferred from the absence of vascular invasion.

Intraoperative and postoperative MES counts

MES were detected in 94% of cases monitored intraoperatively, 71% of patients at the 0–1 h postoperative phase (median MES count 4), 27% of patients at the 2–3 h postoperative phase, 24% of patients at the 4–6 h phase and 14% of patients at 24 h (median MES counts at other postoperative phases 0). The median values and quartile rankings for MES counts at various operative and postoperative phases are shown in Table 2. Ranges of MES counts are illustrated in Fig. 1.

Intraoperative MES counts of greater than 10 during any phase were noted in 18 cases (24%). Thirteen of these occurred in the 30 s immediately following either clamp removal and restoration of shunt flow or clamp removal after arteriotomy closure. During both these
periods air microembolism is a well recognised occurrence\textsuperscript{7,10} and is likely to have a lower potential for inducing ischaemic injury in comparison to particulate embolism.\textsuperscript{18-20} Five patients showed MES counts greater than 10 during stages where particulate embolism is a likely cause for the MES detected (preclamp dissection and wound closure).

Postoperative MES counts of greater than 50/h occurred in eight patients (10\%) at the 0–1 h phase, in one patient at the 2–3 h phase and in one patient at the 4–6 h phase. The latter two patients showed MES counts of 48/h and 54/h, respectively, at the 0–1 h phase. In comparison to the baseline of the time-adjusted median preoperative MES count, there were significantly increased MES noted during the two clamp release phases (Mann–Whitney U, \( p < 0.0001 \)) and wound closure (Mann–Whitney U, \( p = 0.002 \)). Postoperatively, only the 0–1 h phase showed a significant increase in MES counts above the preoperative baseline (Mann–Whitney U, \( p < 0.0001 \)).

High MES loads were not associated with the use of patch angioplasty (Fisher’s exact, \( p = 0.65 \)) or the administration of protamine for reversal of intraoperative heparin therapy (Fisher’s exact, \( p = 0.67 \)). Operative angiographic results were available in seven of the eight cases with frequent postoperative MES. A suboptimal operative result, as defined by a postoperative stenosis of greater than 30\% by the European carotid surgery trial stenosis measurement system,\textsuperscript{7} was not associated with the subsequent occurrence of MES counts over 50/h postoperatively (Fisher’s exact, \( p = 0.17 \)).

In one case with greater than 50 MES/h and associated cerebral ischaemia, the carotid artery was re-explored. White thrombus adherent to the endarterectomised surface was removed, no technical imperfection in the ICA was noted, and patch angioplasty performed. The other high MES load cases were treated with full-dose intravenous heparin, 10\% dextran 40, or a combination of these therapies. Early postoperative carotid duplex ultrasound scanning in three cases did not identify thrombus on the endarterectomy bed.

Reliability of MES reporting

The proportion of agreement between three independent blinded observers for MES occurring at the same points in time over 60 min of monitoring was 0.83 (total of 61 MES counted by one or more observers). The single observer test/re-test reliability for
MES reported at the same points in time over 60 min of monitoring showed a proportion of agreement of 0.80. The correlation between 0–1 h postoperative MES counts reported off-line and on-line in 48 patients was excellent \( (r=0.99) \).

**Discussion**

Spencer and colleagues\(^6\) first observed that cerebral ischaemia in the early postoperative period following CEA may be preceded by frequent MES. Subsequently, further reports have suggested an association between frequent postoperative MES and cerebral ischaemia\(^8,12\) and between intraoperative MES neuropsychological impairment.\(^1,11\) We aimed to assess further the clinical neurological sequelae of intraoperative and postoperative TCD-detected microembolism.

During the various operative phases examined, our results demonstrate that MES are detected at highest rates in the first postoperative hour where counts of greater than 50/h occurred in 10% of patients. MES counts exceeding the hypothetical 50/h threshold were strongly associated, by univariate analysis, with the development of clinical signs of cerebral ischaemia within a time frame of approximately 1 h following their detection. The predictive value of MES counts greater than 50/h and the temporal profile of the development of clinical signs of ischaemia suggest embolus detection may be of practical value for the early identification of patients at high risk of postoperative embolic cerebral ischaemia. These findings support the observations of Gaunt et al.\(^11,13\) that ‘persistent’ MES in the postoperative phase can be an indicator of incipient carotid artery thrombosis and can herald cerebral ischaemia.

The incidence and frequency of MES declined progressively after the first postoperative hour, with two patients only developing high counts during the second or third monitoring period. In no case was MES detected at a frequency of less than 50/h associated with the development of clinical evidence of cerebral ischaemia following an initially normal or unchanged neurological examination. Measures of subclinical ischaemia, however, such as MR brain scanning, were not systematically used in this study.

As noted by other investigators, there are high risk operative stages for the occurrence of MES.\(^7,10-12\) However, despite embolism occurring during up to 92% of operations,\(^11\) the majority of Doppler-detected emboli appear to be of low pathogenicity and result in no clinical or radiological evidence of brain injury. We noted MES to be most frequently detected and to occur at significantly higher rates than the preoperative baseline during the two clamp release phases and during the wound closure phase. The presence of MES during the arterial dissection phase or intraoperative MES counts of greater than 10 for any operative phase were not, however, associated with clinical outcome measures. Interpretation of these results should be guarded, in view of the relatively small numbers of outcome events in our series. In a series of 301 cases with similar rates of MES positivity during the operative stages, Ackerstaff et al.\(^12\) noted a significant association between greater than 10 MES during preclamp dissection and the occurrence of intraoperative and postoperative cerebral ischaemia. The further association noted between intraoperative MES and silent brain ischaemia\(^9,12\) suggests that intraoperative MES are an important risk factor for operative morbidity, and that their identification may be useful in helping to guide surgical techniques.

Assumptions as to the nature and the source of embolisation in this study group are based on the evidence from the one case that underwent operative re-exploration; however, the cases reported by Gaunt et al.\(^11,13\) also implicate platelet embolisation from the endarterectomy bed. Although surgical imperfection is a potential cause for early thrombosis on the endarterectomised surface, a suboptimal operative angiographic result was only noted in one of the eight cases with high MES loads.

Intraoperative monitoring did identify a likely haemodynamic disturbance in the one patient who sustained a major disabling stroke. In all other cases, mean MCA blood flow velocities greater than 50% of the preclamping measurement were maintained throughout the procedure, either via shunt insertion or by collateral flow.

The on-line reporting of MES in the recovery room during the initial 30-minute monitoring session correlated well with off-line reporting, suggesting the online technique can be applied with acceptable accuracy in the clinical setting. The test/re-test and inter-observer agreement on MES counts also suggests reporting of acceptable reproducibility within our centre.

Although TCD signal quality intraoperatively and postoperatively can be degraded by probe and patient movement, the dramatic frequency of MES detected in the patients who subsequently developed ischaemia allowed the sonographer to readily identify high risk patients by the bedside. The focal neurological signs that evolved were also obvious at more detailed neurological examination; however, all patients were assessed prospectively at frequent intervals over the first 24 h by a neurologist. It is likely that a proportion of
the ischaemic neurological events identified in this series may not have been identified by a surgical audit at 30 days postoperatively. 2° TCD monitoring in the early postoperative course of carotid endarterectomy has the potential to identify a population at high risk of embolic stroke. Further studies in this setting examining preventive strategies and interventions are required.

Acknowledgements

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