Are Spontaneous Cerebral Microemboli Consistent in Carotid Disease?

Suzanne Hutchinson, BSc (Hons); Graham Riding, FRCS; Stuart Coull, MB ChB; Charles N. McCollum, MD

Background and Purpose—Transcranial Doppler may be used to detect spontaneous cerebral emboli (SCE), but this information will only identify at-risk patients if these individuals are consistently identified over time. We investigated the consistency of SCE production in patients with symptomatic carotid disease.

Methods—Transcranial Doppler signals from the ipsilateral middle cerebral artery in 25 patients with symptomatic carotid stenosis of >70% were recorded over 1 hour for blind analysis by a panel of trained observers. This was repeated at the same time of day, weekly, for 6 weeks.

Results—The number of patients with SCE increased with each week of monitoring until 13 (52%) were positive. The range of the cumulative number of SCE was 1 to 6. Ten (40%) patients were positive for SCE during only 1 monitoring session, and 2 (8%) were positive for SCE during 2 sessions. SCE-positive patients tended to have more recent symptoms. The correlation coefficients between time elapsed since last cerebral symptom and SCE were weak and not significant.

Conclusions—Most, if not all, patients with severe carotid disease will eventually produce SCE. However, the production of an SCE is random, and it is likely that many hours of monitoring are required to determine whether a patient with symptomatic carotid disease is SCE positive. SCE are unlikely to identify at-risk patients but may indicate periods of transiently increased risk in individual patients. (Stroke. 2002;33:685-688.)

Key Words: carotid artery diseases ▪ cerebral embolism ▪ reproducibility of results ▪ ultrasonography, Doppler, transcranial

Carotid endarterectomy (CEA) is indicated for symptomatic patients with internal carotid artery stenosis >70%. Both the European Carotid Surgery1 trial (ECST) and the North American Symptomatic Carotid Endarterectomy2 trial (NASCET) showed that surgery reduced subsequent stroke risk with an acceptable operative morbidity and mortality. Approximately 14 patients must be operated on to prevent 1 stroke each year, and the cost-benefit ratio for the population as a whole is still disputed.3 A more sensitive method for identifying the patients who are at risk of stroke would reduce the numbers who undergo unnecessary carotid surgery.

Transcranial Doppler (TCD) may be used to detect spontaneous cerebral emboli (SCE) in patients with carotid disease, and the presence of SCE may predict a greater risk of future stroke.4 Their occurrence has been associated with markers of stroke risk, such as recent transient ischemic attack5,6 and plaque ulceration.7,8 However, a marked variability in the number of SCE has been observed in comparable patient populations.4–6,9–11 This may be due to a temporal variability in production, which may be diurnal12 or from one day to the next.5,13 Any investigation to detect patients at increased risk of stroke would need to consistently identify the same at-risk population to be of clinical value.

To determine the consistency of SCE over time, we monitored the ipsilateral middle cerebral artery in symptomatic patients with severe carotid artery stenosis for 1-hour periods at the same time of day, weekly, for a total of 6 occasions.

Subjects and Methods

Twenty-five consecutive patients referred for CEA with a history of transient ischemic attack or stroke and an ipsilateral internal carotid artery stenosis of 70% to 99% were prospectively recruited to the present study. Symptoms included amaurosis fugax, transient ischemic attack, or stroke within the previous 2 years. The severity of carotid stenosis on duplex Doppler imaging was defined by using well-established criteria.14,15 To eliminate other potential sources of SCE, patients with atrial fibrillation, mechanical heart valves, and aortic valve disease were excluded. Patients with ipsilateral internal carotid artery occlusion or restenosis after previous surgery were also excluded. Most patients underwent CEA at the end of the study with little or no delay, because there was a 2-month waiting list at that time. Fully informed consent was taken from each patient, and the study had the approval of the local research ethics committee.

TCD recordings were taken from the middle cerebral artery ipsilateral to the carotid stenosis by using the transtemporal window. A NeuraGuard (Software Version 2.9, Medasonics) system was used with a 2-MHz pulsed-wave Doppler ultrasound probe held in place by a headband. The insonation depth was set individually for each
TABLE 1. Patients With ≥70% Carotid Stenosis (n=25)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total, N</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range), y</td>
<td>72 (59–83)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex, n</td>
<td>19</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ipsilateral ICA stenosis (range), %</td>
<td>84 (70–99)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median time since last symptom (range), mo</td>
<td>1 (0–22)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous stroke, n</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amaurosis fugax, n</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transient ischemic attack, n</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, n</td>
<td>16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin, n</td>
<td>23</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Other antiplatelet agents, n</td>
<td>0</td>
<td></td>
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</tr>
</tbody>
</table>

ICA indicates internal carotid artery.

Results

The demographic characteristics of the study patients are shown in Table 1. Of the patients taking aspirin, 11 took 75 mg/d, 8 took 150 mg/d, and 4 took 300 mg/d. The number of patients with SCE increased with each investigation. One patient (4%, 95% CI 1% to 20%) was positive the first week; 13 patients (52%, 95% CI 34% to 70%) were positive by the sixth week (Table 2). The cumulative total of SCE over 6 weeks in positive patients ranged between 1 and 6. SCE-positive patients were not significantly different from those who were SCE negative or positive on only 1 session regarding any of the variables listed in Table 1.

<table>
<thead>
<tr>
<th>Week</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCE positive, n (%)</td>
<td>1 (4)</td>
<td>4 (16)</td>
<td>6 (24)</td>
<td>10 (40)</td>
<td>12 (48)</td>
<td>13 (52)</td>
</tr>
</tbody>
</table>

Figure 1 shows the number of SCE produced each week for the 13 SCE-positive patients. The distribution of the signals is completely random, with no discernible pattern in their occurrence. Three patients had bursts of SCE during a single hour but then did not produce SCE during 5 other monitoring sessions. One patient produced 3 SCE, 1 patient produced 5 SCE, and another patient produced 6 SCE. These patients, with multiple SCE in a single hour, also did not differ significantly in their characteristics from patients who produced only 1 SCE or were SCE negative.

SCE and Time Elapsed Since Last Symptoms

Patients who were SCE positive tended to have more recent symptoms, with the median time since the last symptom being 1 month compared with 1.5 months for those who were SCE negative. However, this did not approach statistical significance (P = 0.98, Mann-Whitney U test). The correlation coefficients between time elapsed since last cerebral symptom and SCE were weak whether they were measured as total SCE (r = 0.118, Spearman) (Figure 2), the maximum number of SCE in 1 hour (r = 0.067), or SCE per hour (r = 0.534). Thirteen patients (52%, 95% CI 34% to 70%) had their first monitoring session within 1 month of the qualifying event. Of these patients, only 1 (8%, 95% CI 1% to 33%) went on to become positive for SCE on 2 occasions, whereas 2 patients (16%, 95% CI 5% to 45%) who underwent monitoring >1 month after the qualifying event were positive for SCE on ≥2 occasions. Patients who underwent their first monitoring session within 1 month of the qualifying event were not significantly different from those who were monitored for SCE >1 month after the qualifying event whether SCE were measured as total SCE, the maximum number of SCE in 1 hour, or SCE per hour.
who were at lower risk (symptoms some months previously) of further events. We expected that SCE would be produced when carotid disease was active, such as shortly after an event.\textsuperscript{4,6,11} Because we were investigating whether SCE consistently identify the same population of at-risk patients, we also included patients for whom we expected the chance of SCE to be low. In this way, we would be better able to determine whether TCD monitoring can continually distinguish high-risk from low-risk patients.

Our results demonstrate that individual patients cannot be classified reliably as SCE positive or negative because their status changes over time. We would not expect to find any SCE in patients with healthy carotid arteries and no symptoms of cerebral ischemia, but in patients with symptomatic carotid disease, SCE are virtually random. How will it be possible to draw up a protocol to identify patients as SCE positive or negative when new SCE are still being identified during the sixth hour of monitoring? Our data suggest that additional sessions will simply identify more positive patients and that TCD may identify limited time periods during which individual patients are at greater risk.

It is clear that patients are not either SCE positive or SCE negative. A more realistic interpretation of these data is that all patients with significant carotid disease are at risk of SCE and stroke. Carotid atheroma is constantly changing and may be unstable from time to time. Perhaps the risk of stroke is higher at times when these plaques are discharging atherosclerotic material and when, presumably, SCE will also be detectable. The present study was designed to investigate the consistency of SCE and not the association between SCE and clinical symptoms. The present study sample size was not calculated to examine the clinical relevance of SCE, which would have required a much larger sample size. We have demonstrated reliably that there is a lack of consistency in SCE production in patients with carotid disease. A very much larger study would be needed to investigate whether SCE transiently increase the risk of stroke in individual patients. However, the present study has shown that patients are not consistently SCE positive or negative; thus, it would be impossible to identify those at increased risk of stroke. TCD detection of SCE may conceivably indicate periods of transiently increased risk in individual patients.

**References**


**Discussion**

This is the first study attempting to test consistency by repeated investigations of patients with symptomatic carotid stenosis. Stenoses of the internal carotid artery were graded by duplex Doppler imaging with the use of well-established criteria.\textsuperscript{14,15} Most major vascular centers now use only duplex imaging to assess stenoses, and we rarely perform angiography, even digital subtraction angiography, for carotid disease. Our vascular laboratory team has validated their methods against angiography in the past. Our findings demonstrate that most, if not all, patients with severe carotid disease will produce SCE over time. This finding is consistent with previous studies that have demonstrated increasing numbers of SCE over time.\textsuperscript{5,12,13}

There was no significant relationship between time elapsed since the last cerebral symptom and SCE whether the data were analyzed by using total SCE, the maximum number of SCE in 1 hour, or the presence or absence of SCE. An inverse relationship between the number of SCE per hour and time elapsed since the last symptoms has previously been reported.\textsuperscript{4,6,13} Additionally, the prevalence of SCE detected in the present study was lower than the prevalence detected in previous studies; only 1 (4%) of our 25 patients produced SCE in the first hour of monitoring. Previous studies, with monitoring between 20 and 60 minutes in comparable patient populations, reported a prevalence ranging from 28% to 52%.\textsuperscript{4,6,10,13,17} We used objective criteria and a panel of 3 trained observers. Furthermore, the prevalence of SCE at each of the 6 visits was similar, demonstrating that the strict criteria used in the interpretation of the TCD recordings produced a relatively consistent prevalence in this population. Patients who were SCE positive were not significantly different from patients who were SCE negative in terms of time elapsed since the last symptoms, symptom type, and plaque appearance. Associations between these factors and the presence of SCE have all been reported previously.\textsuperscript{4,6,8,11,13}

The selection of patients for the present study included those who were at high risk (recent symptoms) and those...


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