Asymptomatic Embolization Predicts Stroke and TIA Risk in Patients With Carotid Artery Stenosis

Jane Molloy, MRCP; Hugh S. Markus, DM

Background and Purpose—Improved methods of identifying patients at high risk of thromboembolism would allow improved targeting of therapy. One such situation is carotid artery stenosis. This is associated with an increased risk of stroke, which can be reduced by carotid endarterectomy. However, the risk-benefit ratio is low in patients with tight asymptomatic stenosis and moderate symptomatic stenosis. Most stroke in patients with carotid stenosis is believed to be embolic. Therefore, the detection of asymptomatic cerebral emboli using Doppler ultrasound may allow identification of a high-risk group.

Methods—Transcranial Doppler ultrasound was used to record for 1 hour the ipsilateral middle cerebral artery in 111 patients with >60% carotid artery stenosis (69 symptomatic, 42 asymptomatic). The Doppler audio signal was recorded onto digital audio tape for later analysis for embolic signals (ES) by an individual blinded to clinical details. In 67 subjects the relationship between ES and angiographically determined plaque ulceration was investigated. All subjects were followed up prospectively, and the relationship between ES and risk of future ipsilateral carotid artery territory ischemic events (TIA and stroke) was determined.

Results—ES were detected in 41 (36.9%) subjects. In symptomatic patients there was a significant inverse relationship between the number of ES per hour and time elapsed since last symptoms (Spearman’s ρ = −0.2558, P = 0.034). ES were more common in subjects with plaque ulceration, with a relative risk of 4.94 (95% CI, 1.23 to 19.84; P = 0.025) after controlling for both symptomatic status and degree of stenosis. The presence of ES at entry was predictive of TIA and stroke risk during follow up in both symptomatic (P = 0.02) and asymptomatic patients (P = 0.007). Considering all 111 patients, the presence of asymptomatic embolization was predictive of a further ischemic event, with an adjusted OR of 8.10 (95% CI, 1.58 to 41.57; P = 0.01) after controlling for other cardiovascular risk factors, degree of stenosis, symptomatic status, and aspirin or warfarin use.

Conclusions—Asymptomatic embolization in patients with carotid artery stenosis correlates with known markers of increased stroke risk and is an independent predictor of future stroke risk in patients with both symptomatic and asymptomatic carotid stenosis. It may allow identification of a high-risk group of patients who will particularly benefit from carotid endarterectomy. A large multicenter study is now required to confirm these findings. (Stroke. 1999;30:1440-1443.)

Key Words: carotid artery diseases ■ cerebral embolism ■ stroke ■ ultrasonography

Improved methods of identifying patients at high risk of thromboembolism from a variety of sources, including cardiac disease, aortic arch atheroma, and carotid artery stenosis, are required. This would allow more effective targeting of therapy and improve risk-benefit therapeutic ratios. One such situation is carotid artery stenosis, which accounts for approximately one quarter of all strokes. Two large international studies1,2 have demonstrated that carotid endarterectomy reduces stroke risk in recently symptomatic patients with internal carotid artery stenosis of >70%. In patients with moderate symptomatic stenosis the increased stroke risk is lower, and operating on this group of patients as a whole does not improve outcome.3 Similarly, operating on an unselected group of patients with asymptomatic carotid stenosis of >60% appears to have limited benefit. Although there was a significant reduction in stroke risk in a recent study, this reduction was small: 17 patients would have to be operated on to prevent 1 stroke over a 5-year period.4 In routine practice the benefit may be even less; although the perioperative stroke rate in this study was very low at only 1%, it is likely to be higher in routine clinical practice.

A clear implication of these results is that better methods are required to identify patients with carotid stenosis who are at high risk of stroke, particularly among those with tight asymptomatic carotid stenosis and moderate symptomatic carotid stenosis.5 A number of markers of increased risk have been suggested, including the degree of stenosis, plaque ulceration determined angiographically, brain infarction on
neuroimaging, echoluent plaque determined ultrasonically, and impaired intracerebral hemodynamics. An additional promising method is the detection of asymptomatic embolization through use of transcranial Doppler ultrasound. Amurolia fugax and transient ischemic attack (TIA), which are associated with increased risk of subsequent stroke, are believed to be caused by embolization in the majority of cases. Therefore, it is possible that asymptomatic cerebral emboli may have a similar predictive value.

Since the early 1990s it has been appreciated that solid cerebral emboli, composed of thrombus and platelet aggregates, can be detected with transcranial Doppler ultrasound. A number of studies have demonstrated that asymptomatic embolization is frequent in the ipsilateral middle cerebral artery (MCA) of patients with carotid artery stenosis. Cross-sectional studies have suggested that such embolic signals (ES) are clinically important, being more common in patients with symptomatic stenosis, recent symptoms, and recent symptoms. However, there are very limited data determining the predictive value of such ES.

In this study we monitored for asymptomatic embolization in 111 patients with either asymptomatic or symptomatic carotid stenosis. We correlated the presence of ES with known markers of increased risk, including plaque ulceration, symptomatic status, and recent symptoms. In addition, we prospectively followed all patients to determine whether the presence of ES during a single 1-hour recording predicted subsequent stroke and TIA risk.

**Subjects and Methods**

One hundred twenty-three consecutive patients presenting with >60% carotid stenosis, determined with standard Duplex ultrasound criteria, and no obvious cardiac embolic source were prospectively recruited to the study. All carotid duplex studies were performed in 1 laboratory by 1 of 2 vascular technicians whose accuracy, using the above criteria, had previously been validated against angiography for 160 carotid bifurcations. Of these, successful insonation of the ipsilateral MCA was possible in 111. Symptomatic patients (n=69) were defined as having had symptoms (amaurolia fugax, TIA, or stroke) in the territory of the stenosed artery within the previous 12 months. Mean+SD time since last symptom was 79.58±85.14 days (range, 1 to 325 days). Forty-two asymptomatic patients were also studied. Thirty-five patients had bilateral stenosis. In these cases the symptomatic stenosis, or in asymptomatic patients the side with a greater degree of stenosis, was studied. Seventy-four patients (66.7%) underwent carotid angiography. In 67 patients the resulting films were of sufficient quality to allow determination of presence or absence of plaque ulceration or irregularity. Of these subjects, 56 were symptomatic and 11 asymptomatic. Plaques were categorized as ulcerated, irregular, or smooth, according to the criteria used in the NASCET trial. The presence of ulceration was determined by an investigator blinded to the results of the transcranial Doppler recordings. During follow-up, 2 patients were treated with warfarin without an antplatelet agent, and all other patients were treated with aspirin at doses from 75 to 300 mg/d.

TCD recordings were made from the MCA ipsilateral to the stenosis via the transtemporal route. All recordings were made using a commercially available TCD machine (EME Pioneer 4040) with a 2-MHz probe held in position with an external fixation device. Standard settings were used with a sample volume of 5 mm. Median depth of insonation was 52 mm (range, 46 to 56 mm). Each patient underwent recording for 1 hour.

The Doppler audio signal was recorded onto digital audio tape. Tapes were analyzed at a later date by an experienced investigator blinded to the patient information. At this time the recorded Doppler signal was replayed into the same TCD machine, at the same sweep speed of 5.1 seconds, and 128-point fast-Fourier transform spectral analysis was performed with an overlap of >50%. All analyses were performed blinded to the patient clinical information. ES were identified by their typical visual appearance on the spectral display and their characteristic sound, with the addition of an intensity threshold of >7 dB, with intensity measured by a standard method.

All study subjects were followed up from the time of the first recording to examine the relationship between the presence of ES and risk of ipsilateral carotid artery territory ischemic events. Follow-up was continued until stroke or TIA, death, or carotid endarterectomy or angioplasty, or study completion. All strokes were confirmed by CT or MRI. Because of their different natural histories, symptomatic and asymptomatic patients were analyzed both as a single group and separately. In the symptomatic group, mean+SD time of follow-up was 22.55±20.31 (range, 1 to 76) days. In the asymptomatic group, mean+SD time of follow-up was 258.1±246.9 (range, 2 to 774) days. The relationship between embolic events and subsequent ipsilateral TIA and stroke was determined through Kaplan-Meier analysis (Figure). Censor points were ipsilateral TIA or stroke, carotid endarterectomy, carotid angioplasty, and nonstroke death. Carotid endarterectomy and angioplasty were performed only in symptomatic patients. Data were also analyzed with a Cox
TABLE 1. Relationship Between Degree of Carotid Stenosis Determined Using Duplex Ultrasound and the Presence of Embolic Signals Results are Shown for All Patients and for Asymptomatic and Symptomatic Patients Separately

<table>
<thead>
<tr>
<th>Embolic Signals, by Stenosis Group</th>
<th>Degree of Stenosis Determined by Duplex Ultrasound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>61%–70% 71%–80% 81%–90% &gt;90%</td>
</tr>
<tr>
<td>Absent</td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>4 (22.2%) 13 (48.1%) 18 (47.4%) 6 (21.4%)</td>
</tr>
<tr>
<td>Absent</td>
<td>14 14 20 22</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>3 (33.3%) 8 (50%) 12 (50%) 6 (30%)</td>
</tr>
<tr>
<td>Absent</td>
<td>6 8 12 14</td>
</tr>
</tbody>
</table>

Es were detected in 41 subjects (36.9%). There were no differences in age or the proportion of subjects who were male, current smokers, or treated for hypertension between the 2 groups. Twenty (42.0%) of the 69 symptomatic patients were embolic signal positive, compared with 12 (28.6%) of the 2 groups. Twenty (42.0%) of the 69 symptomatic patients had ES compared with 11 of 19 (57.9%) with 80% to 89% stenosis and 12 of 30 (40.0%) with ≥90% stenosis (P=0.20). Most of the patients undergoing angiography were symptomatic, and in this group ES were detected in the following proportions: 60% to 79% stenosis, 4 of 13 (30.7%); 80% to 89%, 11 of 19 (55.5%); and ≥90%, 11 of 28 (39.3%; P=0.34).

Within the symptomatic group, 9 (13.0%) had recurrent events during the course of follow-up (2 strokes and 7 TIs). Seven of these 9 subjects (77.7%) were ES positive. Within the asymptomatic group, 2 (5.0%) suffered ipsilateral cerebral ischemic symptoms (1 stroke, 1 TIA); ES were detected in both at the time of first examination. By Kaplan-Meier nonparametric survival analysis, a significant association was found between ES and subsequent stroke and TIA in both the symptomatic group (P=0.02) and the asymptomatic group (P=0.007). Considering all 111 patients, the presence of asymptomatic embolization was predictive of a further ischemic event with an OR of 9.57 (95% CI, 2.04 to 44.82; P=0.0041). This remained significant after Cox regression was used to control for age, sex, current smoking, hypertension, diabetes, symptomatic status, and degree of stenosis determined ultrasonically, with an adjusted OR of 9.02 (95% CI, 1.70 to 47.9; P=0.01). Substituting time since last symptoms for symptomatic status and using an arbitrary value of 1000 days for asymptomatic stenoses reduced the OR to 7.01 (95% CI, 1.07 to 45.80; P=0.04). There was no significant independent association between any of the other variables and risk of stroke and TIA (Table 2). Stroke or TIA occurred during follow-up in 4 patients (11.4%) with bilateral stenosis and in 7 patients (9.2%) with unilateral stenosis (P=0.7).

TABLE 2. Relationship between Risk Factors and Subsequent Risk of Stroke and TIA During Follow-Up, Determined by Cox Regression

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>1.003</td>
<td>0.923–1.090</td>
<td>0.931</td>
</tr>
<tr>
<td>Male sex, n</td>
<td>0.959</td>
<td>0.243–3.787</td>
<td>0.952</td>
</tr>
<tr>
<td>Hypertension, n</td>
<td>1.395</td>
<td>0.307–6.342</td>
<td>0.665</td>
</tr>
<tr>
<td>Diabetes, n</td>
<td>1.082</td>
<td>0.179–6.540</td>
<td>0.931</td>
</tr>
<tr>
<td>Current smoker, n</td>
<td>3.089</td>
<td>0.513–18.581</td>
<td>0.217</td>
</tr>
<tr>
<td>Degree of stenosis, %</td>
<td>0.991</td>
<td>0.910–1.079</td>
<td>0.838</td>
</tr>
<tr>
<td>Time since symptoms, d</td>
<td>0.963</td>
<td>0.923–1.004</td>
<td>0.077</td>
</tr>
<tr>
<td>Embolic signals detected, n</td>
<td>7.000</td>
<td>1.071–45.819</td>
<td>0.042</td>
</tr>
</tbody>
</table>

regression to allow controlling for other risk factors. To allow controlling for time since last symptoms, an arbitrary value of 1000 days was used for all asymptomatic stenoses.

Results

ES were detected in 41 subjects (36.9%). There were no differences in age or the proportion of subjects who were male, current smokers, or treated for hypertension between the 2 groups. Twenty (42.0%) of the 69 symptomatic patients were embolic signal positive, compared with 12 (28.6%) of the 42 asymptomatic subjects (P=0.15). ES were detected in 14 (53.8%) of 26 symptomatic subjects with symptoms within the last 3 months (P=0.037 versus asymptomatic subjects). In symptomatic patients there was a significant inverse relationship between the number of ES per hour and time elapsed since last symptoms (Spearman’s ρ=-0.2558, P=0.034).

ES were detected in 9 of 13 patients (69.2%) with ulcerated stenoses, 10 of 23(43.5%) with irregular stenoses, and 9 of 31(29.0%) with smooth stenoses (P=0.047). ES were more common in subjects with plaque ulceration than those with either smooth or irregular stenoses; (relative risk, 4.14 [95% CI, 1.12 to 15.26; P=0.025]). This association remained significant after controlling for both symptomatic status and degree of stenosis with use of logistic regression (relative risk, 4.94 [95% CI, 1.23 to 19.84; P=0.025]).

The relationship between degree of stenosis and presence of ES is shown in Table 1 for all stenoses and also for asymptomatic and symptomatic stenoses separately. In both the symptomatic and asymptomatic groups, there was a trend toward an increased proportion with ES in subjects with 71% to 90% stenosis compared with subjects with a lesser degree of stenosis. In patients with a high degree of stenosis (>90%), ES appeared less frequent. The differences between the 4 degrees of stenosis were significant when all subjects were considered (χ², P=0.034) but not when only asymptomatic (P=0.058) or symptomatic (P=0.470) subjects were considered. A similar trend was seen when stenosis was determined angiographically by the ECST method, although the overall numbers of subjects were smaller and the trends not significant. Six of 20 subjects (30.0%) with 60% to 79% stenosis had ES compared with 11 of 19 (57.9%) with 80% to 89% stenosis and 12 of 30 (40.0%) with ≥90% stenosis (P=0.20). Most of the patients undergoing angiography were symptomatic, and in this group ES were detected in the following proportions: 60% to 79% stenosis, 4 of 13 (30.7%); 80% to 89%, 11 of 19 (55.5%); and ≥90%, 11 of 28 (39.3%; P=0.34).

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Discussion

This study provides further evidence of the clinical significance of asymptomatic embolization detected by transcranial Doppler ultrasound in patients with carotid artery stenosis. Consistent with previous studies we found in symptomatic patients an inverse relationship between the number of asymptomatic ES and time since last symptoms.9,10 This is consistent with natural history data which have shown that stroke risk is reduced in the first 1 to 2 years after TIA or minor stroke, after which it approaches the level found in asymptomatic carotid stenosis.17 Furthermore, we confirmed...
the previously reported association between plaque ulceration, determined histologically and angiographically, and asymptomatic embolization. In a subgroup analysis from the NASCET trial, plaque ulceration determined angiographically was found to be a strong predictor of subsequent risk.

While these associations suggest that asymptomatic emboli have a clinical significance, this can be proved only in prospective studies. The results of our prospective follow-up provide preliminary data that the presence of asymptomatic embolization does indeed predict future stroke and TIA risk. There have been few previous prospective studies in this area. One small study in patients with asymptomatic carotid stenosis suggested that the presence of 2 or more emboli per hour predicted subsequent stroke and TIA risk. Our results suggest that the presence of ES is an independent predictor of future clinical embolic events. The independent relationship persisted after controlling for time since last symptoms, which itself is significantly related to the presence of ES.

Our results suggest an increase in the prevalence of distal embolization until a stenosis of approximately 90% is reached but a reduced risk of embolization with very tight stenoses. There were no ES at all in asymptomatic patients with >90% stenosis. A tight stenosis can be accompanied by reduced flow and distal internal carotid artery collapse, and this might be expected pathophysiologically to confer reduced risk. This is consistent with data from the NASCET trial, demonstrating a reduced risk of stroke above stenoses with distal ICA collapse compared with 90% stenoses without distal collapse.

Although our results represent the largest prospective study to date, a number of reservations need to be made in interpreting the data. The results suggest that asymptomatic embolization, detected with transcranial Doppler ultrasound, is a marker of increased risk of subsequent clinical embolization. The technique may allow identification of a high-risk group of patients with carotid stenosis who may particularly benefit from carotid endarterectomy. However, the confidence intervals of our risk estimates are wide, and therefore the findings need to be replicated in a much larger multicenter study. Our power calculations suggest that a sample size of approximately 600 patients is required for such a study in patients with asymptomatic carotid stenosis. Evidence from such a study is required before this technique can be used to guide selection of patients for carotid endarterectomy.

Acknowledgment
This work was supported by a British Heart Foundation grant (PG95049).

References
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Stroke. 1999;30:1440-1443
doi: 10.1161/01.STR.30.7.1440
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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