Microembolic Signals and Risk of Early Recurrence in Patients With Stroke or Transient Ischemic Attack

Luc Valton, MD; Vincent Larrue, MD; Anne Pavy le Traon, MD; Pierre Massabuau, MD; Gilles Géraud, MD

Background and Purpose—Asymptomatic microembolic signals (MES) can be demonstrated in patients with cerebral ischemia using transcranial Doppler (TCD) ultrasonographic monitoring of the middle cerebral artery. However, the clinical relevance of MES remains uncertain. The purpose of this study was to estimate the independent contribution of microembolism to the risk of early ischemic recurrence (EIR) in patients with stroke or transient ischemic attack (TIA) of presumed arterial origin.

Methods—we studied the incidence of EIR in 73 consecutive patients with carotid stroke or TIA in whom TCD scanning of the symptomatic middle cerebral artery was performed within 7 days from the onset of symptoms. Patients with a potential cardiac source of embolism were excluded from the study.

Results—Eight patients had EIR during a mean±SD follow-up of 10±8 days. The incidence of EIR was 4.3 per 100 patient-days in patients with MES and only 0.5 per 100 patient-days in patients without MES. The presence of MES was a significant predictor of EIR after adjustment for the presence of carotid stenosis or aortic arch atheroma, antiplatelet therapy during follow-up, and other potential confounding variables (relative risk, 8.7; 95% confidence interval, 2 to 38.2; P=0.0015).

Conclusions—Microembolism is a significant independent predictor of EIR in patients with stroke or TIA of presumed arterial origin. (Stroke. 1998;29:2125-2128.)

Key Words: cerebral embolism ■ risk factors ■ stroke, acute ■ ultrasonography

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atients with symptomatic tight carotid stenosis or thick aortic arch atheroma (AAA) are at risk for stroke recurrence.1–3 However, not all the patients with such arterial lesions develop recurrence. Methods that might help to select patients at highest risk would be useful for therapeutic decisions.

Asymptomatic microembolic signals (MES) can be demonstrated in patients with carotid stenosis or AAA using transcranial Doppler (TCD) ultrasonographic monitoring of the middle cerebral artery (MCA).4–7 In patients with carotid stenosis, microembolism has been related to the degree of carotid narrowing8 and to the ulcerated appearance of the plaque.9,10 However, the clinical relevance of MES remains uncertain. In patients with asymptomatic severe carotid stenosis, microembolism has been associated with an increased risk of subsequent stroke or transient ischemic attack (TIA).11 Early microembolism after carotid endarterectomy has also been related to postoperative cerebral ischemia.12 A few studies have suggested that microembolism may be a risk factor for early ischemic recurrence (EIR).13–15 However, none of their designs permitted them to control for the effect of potential confounding variables, such as severe carotid stenosis or thick AAA. The purpose of our study was to assess the independent contribution of microembolism to the risk of EIR in patients with cerebral ischemia of presumed arterial origin.

Subjects and Methods
We followed up 73 patients with stroke or TIA in the anterior circulation. All subjects were selected from a series of 102 consecutive patients who were monitored for MES detection within 7 days from the onset of symptoms. The diagnosis of ischemic stroke or TIA was based on each patient’s clinical presentation and was supported by extensive laboratory investigations including early brain CT scan. Twenty-nine patients were excluded for the following reasons: in 4 patients the symptoms of focal cerebral impairment were not related to an acute cerebral ischemia; ischemia involved the vertebralbasilar territory in 6 patients; 3 patients were not followed up in the Department of Neurology; recordings of the TCD scans were not available for technical reasons in 2 patients; and finally, because we wanted to focus on the risk of recurrence in patients with cerebral ischemia of presumed arterial origin, we excluded 14 patients with a potential cardiac source of emboli (atrial fibrillation, intracardiac thrombus, recent myocardial infarction, valvular disease, or prosthetic valves) as detected by medical history, ECG, and echocardiography.

The mean±SD age of the 73 remaining patients (52 men and 21 women) was 65±13 years (range, 32 to 96 years). Twenty-three patients presented with TIA and 50 with ischemic stroke. The diagnosis of lacune was made in 10 patients with lacunar syndromes.
source of emboli was defined as carotid stenosis of η70% (extracranial in 22, intracranial in 1, and proximal common carotid in 1), carotid dissection (n=6), thick (≥5 mm) atheroma in the ascending or horizontal aorta (n=11), or proximal aortic dissection (n=2). Among the other patients, 15 had no detectable arterial lesion and 17 had a carotid stenosis of <70% (n=14) or an aortic plaque of <5 mm (n=6). A prior recent stroke or TIA was defined as a stroke or a TIA that occurred during the 6 months preceding the qualifying ischemic event.

Unilateral TCD monitoring of the MCA was performed on the symptomatic side for 20 minutes in all patients. TCD monitoring was performed on both MCAs in 33 patients. A repeat examination was performed on the symptomatic MCA during follow-up in 26 patients. TCD studies were performed with a Pioneer 2020 (EME Nicolet). Briefly, after location of the artery, a 2-MHz transducer was attached with an elastic head strap. The depth chosen was from 45 to 50 mm to obtain maximum insolation of the MCA. Then, gain and sample volume were reduced (to 10 mm for the sample volume), and the time window overlap was increased to 72% to obtain better detection of MES. The audible Doppler shift and the fast Fourier–transformed spectra were continuously observed by an experienced investigator, who noted all events that could be sources of artifact. All monitoring sessions were recorded on digital audiotapes and were analyzed off-line by an independent observer who was blinded to the clinical data. High-intensity transient signals of an intensity of ≥6 dB were selected first. Measurement of the peak intensity of each signal was performed by visually “thresholding” the intensity of the spectral display in 1-dB increments using the instrument gain-setting adjustment. Intensities were averaged for each signal over 3 replays of the tape. The diagnosis of MES was made among these selected signals in agreement with international recommendations: unidirectional, within the blood flow velocity spectrum, short duration (<0.15 and <0.3 seconds for systolic and diastolic signals, respectively) signals accompanied by a characteristic sound, occurring randomly within the cardiac cycle and without any simultaneous detectable source of artifact. To assess the interobserver agreement for the diagnosis of MES among transient signals of an intensity of ≥6 dB, the recordings of 32 patients were analyzed by a second independent observer. The patients received the following antithrombotic treatments when TCD scanning was performed: 46 patients were treated with an antiplatelet agent (250 mg aspirin in 43, 500 mg ticlopidine in 3). Most of them also received an anticoagulant (low dose in 14 patients, full dose in 30 patients); 17 patients received only an anticoagulant (low dose in 8 patients and full dose in 9 patients). Ten patients received no antithrombotic treatment.

Duration of follow-up was reduced to the time of hospitalization in our Department of Neurology. This was done because 11 patients had early carotid endarterectomy following their ischemic event. Two other patients had prompt surgical repair of aortic dissection.

**Table.** Characteristics of Patients at Entry

<table>
<thead>
<tr>
<th></th>
<th>With MES (n=15)</th>
<th>Without MES (n=58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SD, y</td>
<td>66±13</td>
<td>65±13</td>
</tr>
<tr>
<td>Men</td>
<td>11 (73)</td>
<td>41 (71)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9 (60)</td>
<td>32 (55)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2 (13)</td>
<td>13 (22)</td>
</tr>
<tr>
<td>Smoking</td>
<td>7 (47)</td>
<td>30 (52)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>9 (60)</td>
<td>25 (43)</td>
</tr>
<tr>
<td>Recent prior stroke or TIA</td>
<td>8 (53)</td>
<td>14 (24)*</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>5 (33)</td>
<td>20 (34)</td>
</tr>
<tr>
<td>Carotid source of emboli</td>
<td>11 (73)</td>
<td>19 (33)†</td>
</tr>
<tr>
<td>Aortic source of emboli</td>
<td>4/7 (57)</td>
<td>9/42 (21)†</td>
</tr>
<tr>
<td>Arterial source of emboli</td>
<td>14 (93)</td>
<td>27 (47)§</td>
</tr>
<tr>
<td>Lacune</td>
<td>1 (7)</td>
<td>9 (16)</td>
</tr>
<tr>
<td>Large stroke</td>
<td>3 (20)</td>
<td>8 (14)</td>
</tr>
<tr>
<td>Cortical infarct</td>
<td>3 (20)</td>
<td>10 (17)</td>
</tr>
<tr>
<td>Subcortical infarct</td>
<td>2 (13)</td>
<td>8 (14)</td>
</tr>
<tr>
<td>TIA</td>
<td>5 (33)</td>
<td>18 (31)</td>
</tr>
<tr>
<td>Antiplatelet therapy</td>
<td>9 (60)</td>
<td>37 (64)</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>14 (93)</td>
<td>47 (81)</td>
</tr>
<tr>
<td>Full-dose anticoagulation</td>
<td>6 (40)</td>
<td>32 (55)</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages. *P=0.055; †P=0.007; ‡P=0.02; §P=0.001.

With this definition, mean±SD follow-up was 10±8 days. EIR was defined as either ischemic stroke or TIA that occurred after the first TCD monitoring, and was diagnosed during hospitalization in our department by the attending neurologist before discharge, carotid endarterectomy, or aortic surgery. In patients with previous stroke, recurrence was defined as a sudden clinical deterioration with a decrease of at least 2 points on the Scandinavian Stroke Scale caused by either worsening of the initial deficit or a new focal deficit. Hemorrhagic transformations and brain edema were excluded by brain CT scan. Antithrombotic treatment at the time of EIR or at the end of follow-up in patients without EIR consisted of an antiplatelet agent in 67 patients (aspirin in 56 patients, ticlopidine in 8 patients, and ticlopidine and aspirin in 3 patients) associated in all but 2 with an anticoagulant (low dose in 40, full dose in 25) and an anticoagulant alone in 6 patients (low dose in 4, full dose in 2).

The interobserver agreement for the diagnosis of MES was calculated with the κ statistic. Univariate analysis was performed using the χ² test with continuity correction and 2-tailed Fisher’s exact test for categorical variables and Student’s t test for continuous variables. Tests were bilateral. The probability of survival free of EIR according to the presence of MES at entry was estimated with the Kaplan-Meier method. Kaplan-Meier curves were compared with use of the log-rank test. To calculate the adjusted relative risk of EIR in the presence of MES, we used a Cox model that included carotid stenosis or aortic arch atheroma, large stroke, lacune, prior stroke or TIA, and antiplatelet therapy during follow-up. A stepwise procedure allowed only significant variables to be retained in the final model. Significance was set at P<0.05. Data were analyzed with SAS software.

**Results**

Characteristics of patients at entry are summarized in the Table. Fifteen patients had MES on the first TCD scanning of the symptomatic MCA. The mean±SD time between the qualifying ischemic event and the TCD scan was 2±2 days. The κ index for the diagnosis of MES was good (κ=0.895).
TCD monitoring of the symptomatic MCA demonstrated

In this study, patients with recent cerebral ischemia in whom
P had a history of prior recent stroke or TIA (P = 0.055).
Arterial sources of emboli were more common in patients
with MES (93%) than in those without MES (47%, P = 0.001). A carotid source of emboli was found in 11
patients with MES (73%) and in 19 patients without MES
(33%, P = 0.007). An aortic source of emboli was found by
TEE in 4 of 7 patients with MES (57%) and in 9 of 42 patients
without MES (21%, P = 0.02). There were no significant
differences between the 2 groups for cerebral ischemia
patterns and antithrombotic treatments received when TCD
 monitoring was performed.

In the 33 patients who had a bilateral TCD scan, MES were
more frequently found on the symptomatic side (24%) than
on the asymptomatic one (3%, P = 0.03). Among the 26
patients with repeat TCD scanning of the symptomatic MCA,
MES were found in 7 patients on the initial monitoring. The
results of the second monitoring were different from the first
results in 4 patients: MES appeared in 1 patient, but were no
longer present in 3 others. The time between both scans was
3 ± 3 days.

EIR occurred in 8 patients. EIR comprised 2 strokes and 6
TIAs. All occurred in the same carotid territory as the initial
ischemic event. Six patients had fully recovered from the
initial ischemic event when EIR occurred. One patient had an
ischemic recurrence in the left MCA territory after an initial
anterior cerebral artery stroke. The last patient had sudden
worsening of his initial deficit. Two patients had a second
EIR during follow-up.

Five EIRs occurred in 15 patients with MES (33%), and 3
EIRs occurred in 58 patients without MES (5%, P = 0.008).
The incidence of EIR per 100 patient-days was 4.3 in patients
with MES and only 0.5 in patients without MES. The
Kaplan-Meier curves were significantly different from each
other (Figure). In the Cox model the stepwise procedure
selected the presence of MES (relative risk, 8.7; 95% confidence interval, 2 to 38.2; P = 0.0015) and antiplatelet therapy
during follow-up (relative risk, 0.18; 95% confidence interval,
0.03 to 0.94; P = 0.0221) as significant independent predictors of EIR.

Discussion

In this study, patients with recent cerebral ischemia in whom
TCD monitoring of the symptomatic MCA demonstrated
microembolism were at high risk for subsequent EIR. Most
patients with MES had a potential arterial source of embolism. However, the effect of microembolism on the risk of
EIR was independent from that of severe carotid stenosis or
thick AAA and other potential confounding variables.

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Eight patients with MES (53%) and 14 without MES (24%)
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Discussion

In this study, patients with recent cerebral ischemia in whom
TCD monitoring of the symptomatic MCA demonstrated

In conclusion, our findings suggest that microembolism of the symptomatic MCA in patients with recent carotid stroke
or TIA of presumed arterial origin is a significant and
independent predictor of EIR. This may have important
implications for the monitoring of the effect of secondary preventive therapies in this setting.

Acknowledgments

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References


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