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

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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

Patients 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 narrowing\(^9\)\(^-\)\(^10\) 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 vertebrobasilar 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.
(pure hemiparesis, pure sensory stroke, pure sensory-motor syndrome) and an appropriate small and deep infarct on CT or brain MRI, or in the absence of any demonstrable lesion despite a repeat study. The diagnosis of large stroke was made in 11 patients with a severe deficit (complete hemiplegia with conjugate eye deviations and decreased consciousness) and a large infarct in the MCA territory demonstrated on CT. Among the 29 other patients with ischemic stroke, 13 had a cortical infarct, 10 had a subcortical infarct of >15 mm in diameter, and 6 had no demonstrable lesion on CT or MRI. All patients underwent carotid duplex and TCD scanning. Carotid angiography was performed in 32 patients and MR angiography in 7. Carotid stenoses were graded using the North American Symptomatic Carotid Endarterectomy Trial criteria in patients who underwent angiography, and standard ultrasonographic criteria (peak and teldiastolic velocities and spectral broadening) in the others. Intracranial carotid stenosis, proximal common carotid stenosis, and carotid dissection were diagnosed by angiography after duplex and TCD screening. Severe atherosclerosis and dissection of the proximal aorta were diagnosed by transesophageal echocardiography (TEE), performed in 49 patients, using a biplane or multiplane 5-MHz probe (Hewlett-Packard Sonos 1000). The diagnosis of aortic dissection was confirmed by chest CT scan. A potential arterial source of emboli was defined as carotid stenosis of >70% (extracranial in 22, intracranial in 1, and proximal common carotid in 1), carotid dissection (n=6), thick (>5 mm) atheroma in the ascending aorta in the ascending or horizontal aorta (n=11), or proximal aortic dissection (n=2). Among the other patients, 15 had no demonstrable 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 insonation of the MCA. Then, gain and sample volume were reduced (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 monitorings 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 adjustments. 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.

With this definition, mean±SD follow-up was 10±6 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 $\kappa$ statistic. Univariate analysis was performed using the $\chi^2$ 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 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 $\kappa$ index for the diagnosis of MES was good ($\kappa$=0.895).
Eight patients with MES (53%) and 14 without MES (24%) 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. These results were obtained in a selected population of patients with cerebral ischemia of presumed arterial origin. They cannot be generalized to the patients with a potential cardiac source of embolism, because the incidence and the clinical significance of MES and the risk of EIR may be different in these patients.

Analysis of endarterectomy specimens has demonstrated that microembolism before surgery is closely related to ulceration of the carotid plaque. An appearance of ulceration on carotid angiogram has also been associated with microembolism, whatever the degree of carotid narrowing. On the other hand, in a recent study there was no relationship between microembolism and morphological features of thick aortic plaques of presumed embolic potential on TEE. However, only 19 patients were included in that study. These results and our own findings suggest that consideration of microembolism allows recognition of a subset of patients with unstable arterial sources of embolism and at high risk for EIR.

Antiplatelet therapy was a significant negative predictor of EIR in our study. This finding is consistent with the results of recent clinical randomized trials which suggest that aspirin modestly but significantly reduces the risk of EIR in stroke patients.

We found MES in 22% of patients with recent cerebral ischemia. The rate of MES in previous studies of similar patients has varied from 9% to 71%.[13,14,22–27] Some methodological reasons may account for these discrepancies. Distinction of MES from artifacts or random fluctuations of background Doppler signal may be difficult, especially when a low-intensity threshold for MES detection is used. Besides, one cannot exclude the possibility of an unintentional bias favoring the diagnosis of MES, when the observer is aware of the presence of a potential source of embolism. In our study, we chose an intensity threshold that should reject most normal Doppler speckles, and all recordings were reviewed by investigators blinded to clinical data. Using these methods we obtained good interobserver agreement for the diagnosis of MES. A recent study has demonstrated that such methods, with an intensity threshold of $\pm 6$ dB, permit a good probability of agreement ($0.872$) between observers from different centers.

We used a short duration of testing because stroke patients are often restless and uncooperative. Short durations of testing may be inappropriate to allow diagnosis of random fluctuations of microembolism. Moreover, repeated recordings permit detection of more patients with MES.[6,25] In our study, analysis of a second recording increased the proportion of patients with MES from 7 of 26 to 8 of 26. Hence, although we probably missed some patients with MES, we believe that this occurrence was rare.

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.

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References
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