Microembolic Signal Predicts Recurrent Cerebral Ischemic Events in Acute Stroke Patients With Middle Cerebral Artery Stenosis

Shan Gao, MD; Ka Sing Wong, MD; Tjark Hansberg, MD; Wynnie W. M. Lam, MD; Dirk W. Droste, MD; E. Bernd Ringelstein, MD

Background and Purpose—Cerebral embolism is a common cause of stroke. Microembolic signals (MES) detected by transcranial Doppler represent ongoing embolisms, but the lack of reliable data about its clinical relevance hinders its widespread use in clinical practice.

Methods—We prospectively monitored 114 consecutive acute ischemic stroke patients with middle cerebral artery (MCA) stenosis for MES. The signals on digital audio tape were analyzed by an independent observer who was blinded to all other data. All patients were followed-up for the occurrence of recurrent stroke or transient ischemic attack (TIA) in the indexed MCA territory.

Results—MES was detected in 25 (22%) patients. The mean number of MES was 18 (range, 1 to 102). MES were more common in patients with severe stenosis (10/21, 48%) than in those with mild–moderate stenosis (4/26, 15%) (Pearson \( \chi^2 \) \( P = 0.02 \)). During follow-up for a mean of 13.6 months (range, 1 to 32), 12 (12%) patients had further ischemic events (10 strokes and 2 TIAs) in the affected MCA region during follow-up. Among these, 7 (58%) had recurred within 1 month (1 recurred within 1 week, the other 6 patients had recurrences in week 3 or 4 after discharge), 3 within 6 months, 1 within 6 to 12 months, and the remaining 1 recurred after 1 year. The presence of MES was the only predictor of a further ischemic stroke/TIA by Cox regression (adjusted odds ratio, 8.45; 95% CI, 1.69 to 42.22; \( P = 0.01 \)) even after controlling for age, sex, diabetes, hypertension, previous stroke, smoking, and acute treatment.

Conclusions—In acute stroke patients with MCA stenosis, MES predicts further cerebral ischemia. This procedure should be considered as part of routine investigation and might identify a group of patients who are most likely to benefit from antithrombotic treatment. (Stroke. 2004;35:2832-2836.)

Key Words: arterial occlusive disease ■ cerebral ischemia ■ embolism ■ microembolic signals ■ outcome ■ stroke ■ transcranial Doppler

Extracranial carotid artery occlusive disease is a major cause of ischemic stroke in whites. However, intracranial artery occlusive disease, especially middle cerebral artery (MCA) stenosis, is more prevalent in Asians.1–4 Understanding the mechanisms underlying ischemic stroke is crucial for therapeutic decisions. Hemodynamic compromise and artery-to-artery embolism have been suggested as the 2 major underlying mechanisms in patients with internal carotid artery stenosis. Nevertheless, the pathogenesis of ischemic stroke caused by intracranial artery occlusive disease remains unknown.

With the development of transcranial Doppler ultrasound, it is possible to detect an embolus passing through the insonated artery.5–6 It has been suggested that they represent thrombi and platelet fibrin aggregates.6,7 Microembolic signals (MES) are found more frequently in symptomatic than in asymptomatic patients with internal carotid artery stenosis.10–14 Moreover, the clinical significance of embolic signals has also been reported to be an independent predictor of future stroke.15–18 A few studies have reported the presence of MES in acute stroke patients with MCA stenosis,19,20 but not in those with chronic MCA stenosis.21 However, no prospective study of the clinical significance of MES in patients with MCA stenosis has been performed. The aim of this study is to determine the frequency of embolic signals and their clinical significance in patients with MCA stenosis.

Materials and Methods
From \( \approx 1000 \) acute stroke admissions during the study period, 114 consecutive acute stroke patients with MCA stenosis diagnosed by
transcranial Doppler, who were admitted to the Prince of Wales hospital in Hong Kong, were enrolled in this study. All patients were Chinese. In our institution, ~30% of stroke patients did not have an adequate temporal acoustic window for MES monitoring. Eighty-five of the 114 patients had clinical features compatible with a stroke in the stenotic MCA territory. The other 29 patients had experienced clinical symptoms on posterior circulation or on the same side as the stenotic MCA. A computed tomography scan of the head was performed to rule out intracranial hemorrhage in all patients.

Presence of a poor temporal acoustic window, patient in an agitated or confused state, or presence of other potential sources of embolism, such as severe (>50%) carotid stenosis (by continuous wave ultrasound and carotid duplex) or atrial fibrillation were the exclusion criteria. Because the patients had to be examined in the ultrasound laboratory, those who were comatose, unable to comply physically with the examination, required constant bedside monitoring, or were moribund were excluded from the study.

Clinical assessments included relevant medical history, medications administered during hospitalization, and neurological examinations, which were performed by a neurologist. The definitions of the vascular risk factors adopted for this study were as follows: hypertension was diagnosed in patients who had ≥2 readings of systolic blood pressure ≥160 mm Hg or diastolic pressure ≥90 mm Hg documented before the onset of stroke, or a clinical history of hypertension with the use of antihypertensive medication at any time before or at the time of stroke. Diabetes was diagnosed in patients who had a history of diabetes documented by a physician, or were taking insulin or an oral hypoglycemic agent, or had a fasting blood glucose level ≥140 mg/dL, on at least 2 occasions. For smoking status, patients were classified as having never smoked or smoked (including current smokers and ex-smokers).

The severity of neurological impairments of the index stroke was measured using the National Institutes of Health Stroke Scale (NIHSS). According to previous studies,22-25 the present study grouped the NIHSS scores as: 0 to 1 (mild stroke), 2 to 8 (moderate stroke), and ≥9 (severe stroke), which were entered in later analysis as a categorical variable. All patients were treated with antiplatelet therapy on discharge from hospital.

All patients were followed-up regularly for further stroke/transient ischemic attack (TIA) in the relevant MCA stenosis territory. We interviewed the patients and/or their care takers, as well as examined the medical notes of their outpatients and inpatients record. Posterior circulation symptoms or symptoms that occurred outside this MCA territory were not recognized as further strokes. Follow-up was continued until further stroke or death. Recurrent stroke was diagnosed if the event result in a neurological deficit that was clearly different from that of the index stroke or the event involved a different anatomic site from that of the index stroke. Case ascertainment were performed without knowledge of the results of MES monitoring.

**Diagnosis of MCA Stenosis**

For both intracranial and extracranial arteries, including the bilateral internal carotid artery, external carotid artery, common carotid artery, and subclavian arteries, bilateral MCA, anterior cerebral artery, posterior cerebral artery, and sphenoid internal carotid arteries were assessed by a conventional method using the TC 2020 (Nicolet). Bilateral MCAs were insonated through the temporal window for 30 minutes. A 2-MHz bi-gate transducer was fixed to the head with the Marc 500 TC probe fixation head frame (Spencer Technologies). The upstream depth of insonation was targeted at the stenotic segment and the downstream depth was targeted 8 to 10 mm distally. A small sample volume 6 mm in length and a low gain were used. A detection threshold of ≥5 dB was used.22 The machine used a 128-point FFT analysis and used a graded color scale to display the intensity of the received Doppler signal. FFT time frame overlap was 61% to 71%. In addition, data were continuously recorded onto a 4-channel digital audio tape recorder (TA-88; TEAC Corporation) with normal speed. The recorded data were then analyzed by an experienced observer, who was blinded to the clinical and laboratory data. The number of MES during the 30-minute recording was noted. The following definitions for emboli signals were used: typical and audible (click, chirp, whistle) short-duration, high-intensity signal within the Doppler flow spectrum with its occurrence at random in the cardiac cycle, and an intensity increase of ≥5 dB above the background signal.5

**Statistical Analysis**

All data were entered into SPSS version 9.0 for Windows for analysis. The statistical significance was considered at 0.05 and was 2-sided.

Flow velocity difference between MES-positive patients and MES-negative patients was assessed with 1-way ANOVA. The severity of stroke on admission or the course of stroke during hospitalization between MES-positive patients and MES-negative patients was assessed with 1-way ANOVA. The censored data were nonischemic stroke and death. Cox regression analysis was used to assessing the other risk factors.

**Results**

**Baseline Characteristics of Patients**

Their mean age was 65.86 ± 10.59 years, with 69 patients (60.5%) of 65 years or older. Eighty percent of the patients were men. Hypertension (67%) was the most common vascular risk factor. Other risk factors included previous or current smoking (48%), diabetes (33%), and previous stroke (31%). Occlusive lesions in multiple extracranial or intracranial arteries were frequent (61%). After admission, 31% of patients were treated with anticoagulants and 69.3% were

**TABLE 1. Association Between Frequency of MES and Severity of MCA Stenosis**

<table>
<thead>
<tr>
<th>TCD</th>
<th>No. of Patient</th>
<th>No. With MES, (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vs=140–180 cm/s</td>
<td>72</td>
<td>11 (15)</td>
<td>0</td>
</tr>
<tr>
<td>Vs&gt;180 cm/s</td>
<td>42</td>
<td>14 (33)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MRA</th>
<th>No. of Patient</th>
<th>No. With MES, (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild–moderate stenosis</td>
<td>26</td>
<td>4 (15)</td>
<td></td>
</tr>
<tr>
<td>Severe stenosis</td>
<td>21</td>
<td>10 (48)</td>
<td>0</td>
</tr>
</tbody>
</table>

stenosis (30% to 75%) or severe stenosis (>75%) according to the lumen reduction and amount of signal loss.
given antiplatelet agents. All patients were treated with antiplatelet drugs on discharge from hospital. There was no significant association between the presence of MES and age, sex, diabetes and hypertension, smoking, or previous stroke ($P = 0.44, 0.59, 0.64, 0.44, 0.88, \text{and} 0.05$ respectively). The association between therapeutic agent given after admission and the presence of MES was not assessed because treatment and MES monitoring were usually begun on the same day. The median NIHSS on admission was 3 (range, 0 to 18). The median NIHSS on admission was 3 in MES-positive patients and 3 in MES-negative patients. Twenty-five percent of patients had mild stroke, 55% had moderate stroke, and 17% had severe stroke. Among 47 patients who underwent magnetic resonance angiography examination, MES were more common in patients with severe stenosis (10/21, 48%) than in those with mild–moderate stenosis (4/26, 15%) ($\chi^2, P = 0.016$; Table 1).

**Correlation Between the Presence of MES and Further Ischemic Stroke/TIA**

Mean±SD time of follow-up was 13.6 months (range, 1 to 32 months). Twelve (12.2%) patients had further ischemic events (10 strokes and 2 TIAs) in the affected MCA region during follow-up (Table 2). Among these, 7 (58%) had recurred within 1 month (1 recurred within 1 week, the other 6 patients recurred in week 3 or 4 after discharge), 3 within 6 months, 1 within 6 to 12 months, and the remaining 1 recurred after 1 year. Six of these 12 patients (50%) were MES-positive. Nine patients died during follow-up. The causes of death were cerebral hemorrhage on the contralateral side (2 patients), nonvascular disease (eg, cancer or pneumonia in 4 patients), or unknown causes (3 patients). By Kaplan–Meier nonparametric survival analysis, a significant association was found between MES and further incidences of stroke ($\log \text{rank}, 5.96; P = 0.03$). After controlling for age, sex, diabetes, hypertension, smoking, degree of stenosis, previous stroke, and therapeutic agents (anticoagulant or aspirin), the adjusted odds ratio became 8.45 (95% CI, 1.69 to 42.22; $P = 0.01$) (Table 3).

**Discussion**

**Prevalence of MES**

Evidence of artery-to-artery embolism generated from the stenotic MCA to the distal branches has been confirmed histologically.

28 Thromboembolic occlusion in the distal artery has the same composition as the thrombi on the surface of atheromatous plaques of MCA, which contain a large amount of fibrin and platelets. For patients with MCA stenosis, only a few studies have documented the frequency and significance of MES detected by TCD. In 3 patients (21%) with mostly chronic MCA stenosis, MES were detected. In a pilot study, MES were infrequent findings (15%) in

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age</th>
<th>Recurrent Stroke (mo)</th>
<th>Diagnosis</th>
<th>Predominant Symptoms</th>
<th>MES Presence</th>
<th>No. of MES</th>
<th>Peak Flow Velocity (cm/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>60</td>
<td>1</td>
<td>RMCA stenosis</td>
<td>Left hemiparesis</td>
<td>Y</td>
<td>10</td>
<td>165</td>
</tr>
<tr>
<td>M</td>
<td>72</td>
<td>1</td>
<td>Bilateral MCA stenoses</td>
<td>Right hemiparesis</td>
<td>N</td>
<td>0</td>
<td>148</td>
</tr>
<tr>
<td>M</td>
<td>69</td>
<td>1</td>
<td>LICA, MCA; Siphon ICA, VA stenoses</td>
<td>Right hemiparesis</td>
<td>Y</td>
<td>9</td>
<td>180</td>
</tr>
<tr>
<td>M</td>
<td>64</td>
<td>1</td>
<td>LTICA, LMCA, LACA, RMCA stenoses</td>
<td>Right hemiparesis</td>
<td>N</td>
<td>0</td>
<td>153</td>
</tr>
<tr>
<td>F</td>
<td>51</td>
<td>1</td>
<td>Bilateral MCA, siphon ICA stenoses</td>
<td>Left hemiparesis</td>
<td>Y</td>
<td>1</td>
<td>150</td>
</tr>
<tr>
<td>M</td>
<td>57</td>
<td>1</td>
<td>RMCA stenosis</td>
<td>Left hemiparesis (TIA)</td>
<td>Y</td>
<td>102</td>
<td>300</td>
</tr>
<tr>
<td>M</td>
<td>84</td>
<td>1</td>
<td>LMCA, RICA stenoses</td>
<td>Right hemiparesis</td>
<td>Y</td>
<td>20</td>
<td>200</td>
</tr>
<tr>
<td>M</td>
<td>63</td>
<td>4</td>
<td>LMCA and TICA stenoses</td>
<td>Right hemiparesis</td>
<td>N</td>
<td>0</td>
<td>144</td>
</tr>
<tr>
<td>M</td>
<td>74</td>
<td>4</td>
<td>Bilateral MCA stenoses</td>
<td>Left hemiparesis</td>
<td>Y</td>
<td>2</td>
<td>150</td>
</tr>
<tr>
<td>F</td>
<td>65</td>
<td>5</td>
<td>Bilateral MCA, siphon ICA stenoses</td>
<td>Left hemiparesis</td>
<td>N</td>
<td>0</td>
<td>235</td>
</tr>
<tr>
<td>M</td>
<td>52</td>
<td>7</td>
<td>RTICA, LMCA stenoses</td>
<td>Right hemiparesis</td>
<td>N</td>
<td>0</td>
<td>146</td>
</tr>
<tr>
<td>F</td>
<td>68</td>
<td>16</td>
<td>LMCA stenosis</td>
<td>Right hemiparesis</td>
<td>N</td>
<td>0</td>
<td>147</td>
</tr>
</tbody>
</table>

MCA indicates middle cerebral artery; TICA, terminal internal carotid artery; ICA, internal carotid artery; ACA, anterior cerebral artery; Y, yes; N, no; M, male; F, female.

Kaplan–Meier survival plots comparing survival free of further cerebral ischemia with and without MES.
symptomatic acute stroke patients but not in asymptomatic patients with MCA stenosis. Another study also reported the absence of MES in chronic stroke patients with MCA stenosis, Droste et al reported that MES were mainly observed in patients with recent symptomatic intracranial atherosclerosis and severe stenosis only. The short delay between symptoms and TCD may explain the relatively high prevalence of MES in the present study.

Predictive Value of MES for Future Stroke

Previous studies had shown that the presence of MES was predictive of increased risk of future cerebral ischemia in patients with symptomatic or asymptomatic internal carotid artery stenosis, carotid endarterectomy, and patients with stroke or TIA of presumed arterial origin. Retrospective data reported by Babikian et al showed that further cerebral or retinal ischemic events occurred in the territory of MES-positive arteries than in the territory of MES-negative arteries. Molley et al demonstrated that 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. The results of our prospective follow-up study provide the first data to our knowledge that the presence of MES independently predicted future risk of cerebral ischemia in patients with MCA stenosis. These results suggest that stable atherosclerotic MCA stenoses (those without MES) remain silent, whereas unstable MCA stenoses (those with MES) cause further cerebral ischemia. Increased flow velocity, decreased residual lumen, and increased systemic risk factors associated with increased blood thrombogenicity or a systemic hypercoagulable state will increase the risk of thrombosis and subsequent embolization. A retrospective study reported a favorable risk/benefit ratio for warfarin compared with aspirin for the prevention of major vascular events with symptomatic intracranial large-artery stenosis.

In summary, this study confirmed the clinical significance of MES in the acute stage and predicted further cerebral ischemia. Our data support further studies to explore the potential of MES detection as a means to monitor the effect of antithrombotic treatments in stroke patients.

TABLE 3. Relationship Between Risk Factors and Subsequent Risk of Further Stroke/TIA During Follow-up, Determined by Cox Regression

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Unadjusted OR (95% CI)</th>
<th>Unadjusted P</th>
<th>Adjusted OR (95% CI)</th>
<th>Adjusted P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.99 (0.94–1.05)</td>
<td>0.89</td>
<td>0.99 (0.94–1.06)</td>
<td>0.85</td>
</tr>
<tr>
<td>Male</td>
<td>0.75 (0.20–2.81)</td>
<td>0.67</td>
<td>1.58 (0.32–7.89)</td>
<td>0.58</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.52 (0.77–8.25)</td>
<td>0.13</td>
<td>3.35 (0.74–17.22)</td>
<td>0.12</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.42 (0.52–11.18)</td>
<td>0.26</td>
<td>2.57 (0.38–17.22)</td>
<td>0.33</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>0.44 (0.94–2.03)</td>
<td>0.29</td>
<td>0.40 (0.08–2.00)</td>
<td>0.26</td>
</tr>
<tr>
<td>Ever smoking</td>
<td>1.86 (0.57–6.09)</td>
<td>0.31</td>
<td>1.48 (0.28–7.91)</td>
<td>0.64</td>
</tr>
<tr>
<td>Velocity (&gt;180)</td>
<td>0.96 (0.28–3.27)</td>
<td>0.94</td>
<td>0.52 (0.10–2.80)</td>
<td>0.45</td>
</tr>
<tr>
<td>MES positive</td>
<td>3.94 (1.18–13.07)</td>
<td>0.03</td>
<td>8.45 (1.69–42.22)</td>
<td>0.01</td>
</tr>
<tr>
<td>Heparin/aspirin</td>
<td>0.6 (0.16–2.25)</td>
<td>0.45</td>
<td>0.82 (0.60–1.34)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Acknowledgments

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References

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