Progression of Middle Cerebral Artery Occlusive Disease and Its Relationship With Further Vascular Events After Stroke

Ka Sing Wong, MD; Huan Li, MB; Wynnie W.M. Lam, FRCR; Yu Leung Chan, FRCR; Richard Kay, MD

Background—Serial changes of flow velocities of transcranial Doppler ultrasound (TCD) in symptomatic middle cerebral artery (MCA) occlusive disease may be related to the occurrence of further vascular events, but prospective data are lacking.

Methods—We conducted a prospective study on patients with cerebral ischemia who were hospitalized with symptomatic MCA stenosis or occlusion. We repeated TCD examinations 6 months after the initial examinations and recorded any stroke or coronary events during this period. The changes of MCA flow velocities were categorized as normalized artery, stable artery, and progressed artery, which were determined according to the changes of MCA velocities at 6 months.

Results—We studied 143 consecutive patients who had relevant MCA occlusive diseases (107 with stenosis and 36 with occlusion). At 6 months, the velocities in the MCA returned to normal in 42 patients (29%), they were stable in 80 patients (62%), and they progressed in 13 patients (9%). The number of clinical events varied significantly among the 3 groups: there were 2 patients (4.8%) with clinical events in the normal group, 11 patients (12.5%) with clinical events in the stable group, and 5 patients (38.5%) with clinical events in the progressed group (P=0.004). The 18 recurrent events included 10 recurrent strokes, 5 transient ischemic attacks, and 3 acute coronary syndromes.

Conclusions—Progression of MCA occlusive diseases is associated with an increased risk of vascular events. Further studies are required to establish the value of serial TCD examinations in predicting future clinical events. (Stroke. 2002;33:532-536.)

Key Words: arterial occlusive disease ■ cerebral ischemia ■ Chinese ■ prognosis ■ ultrasonography, Doppler

Intracranial atherosclerotic occlusive disease is an important cause of stroke among Asians, Hispanics, and African Americans.1–6 However, data on the natural history of the changes in the hemodynamics of intracranial large-artery occlusive lesions after a stroke remain scarce. Transcranial Doppler ultrasound (TCD) is an established method to diagnose significant stenosis and occlusion of major intracranial arteries.7 Because TCD is a safe and noninvasive procedure, it is a suitable method for serial examinations of a large number of patients. However, few published studies have been prospectively conducted, and a relatively limited number of patients have been included.5–13

The present study sought to evaluate the progression of middle cerebral artery (MCA) occlusive disease based on changes of MCA velocity after 6 months and its relationship with further clinical events.

Subjects and Methods

Subjects

In this prospective study, we recruited consecutive stroke patients who had MCA stenosis or occlusion during the acute phase and who were able to return for a repeated TCD examination after 6 months. The method of screening patients was reported in an earlier publication.14 Briefly, patients admitted with acute cerebral ischemia (including transient ischemic attack [TIA] and cerebral infarct) were recruited, and TCD examinations were performed within 1 week of symptom onset. On admission, the baseline data, including age, sex, medical history, and physical examination, were collected. Scoring of the neurological deficits was assessed by using the National Institutes of Health Stroke Scale (NIHSS). Vascular risk factors were noted particularly for patients with any history of smoking, hypertension, diabetes mellitus, ischemic heart disease, atrial fibrillation, and previous TIA or stroke. Blood biochemistry, blood count test, ECG, and chest x-ray were checked routinely.

Transcranial Doppler Ultrasound

TCD examination was performed with an EME TC2000 (Nicolet). By use of a 2-MHz pulsed range–gated transducer, bilateral MCA was insonated through the temporal windows at a depth of 40 mm to 65 mm, with a 4-mm increment. Other intracranial arteries were also examined. The peak systolic velocity was used to define the presence of stenosis. A peak systolic MCA velocity of <140 cm/s was considered to indicate a normal artery. The degree of stenosis was qualified according to published criteria15 and was graded into 3 categories: grade I (140 to 209 cm/s), grade II (210 to 280 cm/s), and grade III (>280 cm/s).
grade III (>280 cm/s). MCA occlusion was diagnosed if all basal arteries except the MCA in question were detectable or if the asymmetry index of the symptomatic MCA was <−21% compared with that of the contralateral MCA. All patients with abnormal MCA findings were invited to have a repeated TCD examination 6 months later. Follow-up TCD examinations were performed with the same TCD machine and with the use of the same protocol. The operator of the repeated TCD examination was unaware of the occurrence of any clinical events in the preceding 6 months.

Categorization of Changes in MCA Flow Velocities at 6 Months

There has been no published classification of the progression of MCA occlusive disease based on TCD findings. In the present study, we categorized our patients into 3 groups based on the initial and repeated TCD findings. In the “normalized” group, patients had initial MCA stenosis or occlusion, but the flow velocities returned to normal after 6 months. In the “stable” group, we included patients (1) who had the same or lower grading of MCA stenosis, (2) who had persistent MCA occlusion, or (3) who initially had an MCA occlusion, which had recanalized but with persistent stenosis. In the “progressed” group, the initial MCA stenosis was upgraded in severity or had progressed to occlusion.

Clinical Events

We followed the patients for 6 months for further vascular events, including TIA, stroke, or acute coronary syndrome. Acute coronary syndrome included myocardial infarction and angina with positive exercise stress test, thallium scan, or coronary angiography. Patients who had died and patients who were unable or unwilling to come for follow-up TCD examination were excluded.

Statistical Analysis

All analyses were performed by using SPSS/Windows version 9.0 statistical software and GraphPad Instat version 3.00 software; statistical significance was set at P<0.05 (2-sided assessment). Cross tabulations were applied for univariate analysis. The χ² test was used to determine whether there were any differences of the flow velocity and clinical events at 6 months. A multivariate logistic regression model was used to estimate the impact of the progression of MCA occlusive lesions on clinical prognosis.

Results

Among the 345 patients with initial vascular lesions, 32 patients with a relevant lesion in the posterior circulation, 23 patients who had died by 6 months, and 88 patients who did not have an MCA lesion were excluded from the study. Of the remaining 202 patients with initially relevant MCA lesions, 59 patients were unwilling or unable to come for the repeat TCD examination. The remaining 143 patients with relevant MCA lesions constituted the study group. For these patients, the baseline characteristics, the vascular risk factors, and the use of antplatelet agents are shown in Table 1. The vascular risk factors were common among these patients. The most common risk factor was hypertension (61.5%), followed by history of smoking (47.6%). Ninety-seven percent of the patients were discharged on a regimen of antplatelet drug or anticoagulant therapy.

Initial TCD Results

The initial TCD examination was performed within an average of 3.1±2.2 days after symptom onset. MCA stenosis was detected in 107 (75%) of the patients (see Figure 1 for representative magnetic resonance angiography and TCD), and MCA occlusion was detected in 36 (25%) of the patients (see Figure 2 for representative magnetic resonance angiography and TCD). Apart from more ischemic heart disease found among patients with MCA occlusion (P=0.005 by χ² test), there were no significant differences of risk factors between patients with occlusion and patients with stenosis. Compared with patients with MCA stenosis, patients with MCA occlusion tended to have a more severe index stroke (P=0.03 by χ² test). Of the 107 patients with MCA stenosis, 91 (85%) had mild stenosis (grade I), 13 (12%) had moderate stenosis (grade II), and 3 (3%) patients had severe stenosis (grade III). Extracranial carotid ultrasound examination revealed that 35 patients had clinically relevant tandem carotid stenosis. Because of the design of the present study, which
included patients with repeated TCD study, patients who died or were unwilling to return for TCD examination were excluded. Twelve patients with initial MCA stenosis (6 patients) or occlusion (6 patients) were dead by 6 months. These patients tended to be older than the study group (78 versus 64 years, respectively) and had more severe stroke (17% versus 14% with NIHSS >9, respectively). Four patients died of the index stroke, 2 died of recurrent stroke, and 2 died of myocardial infarction.

Fifty-nine patients were unwilling or unable to return for repeated TCD examination. They tended to be older than the study group (70 versus 64 years, respectively) and had more severe stroke than the study group (20% versus 14% with NIHSS >9, respectively). Their initial TCD findings showed that 44 (75%) of the patients had MCA stenosis and that 15 (25%) had MCA occlusion. At 6 months, 6 of the 59 patients suffered a further vascular event, including 3 TIAs, 2 recurrent ischemic strokes, and 1 hemorrhagic stroke.

**TCD Results at 6 Months**
In the TCD examinations at 6 months, the MCA velocity became normalized in 42 patients (29.4%), and the MCA was diagnosed to have stenoses in 86 patients (57.3%) and occlusions in 15 patients (13.3%), as shown in Table 2. Univariate analysis showed that MCA stenosis was associated with diabetes ($P=0.01$ by $\chi^2$ test). Initial TCD showed that 32 patients had MCA stenosis and 8 patients had MCA occlusion.

### Table 2. Results of Initial and Repeated TCD Findings

<table>
<thead>
<tr>
<th>MCA Status</th>
<th>Patients, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial stenosis (N=107)</td>
<td></td>
</tr>
<tr>
<td>At 6-mo TCD</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>27</td>
</tr>
<tr>
<td>Stenosis</td>
<td>75</td>
</tr>
<tr>
<td>Occlusion</td>
<td>5</td>
</tr>
<tr>
<td>Initial occlusion (N=36)</td>
<td></td>
</tr>
<tr>
<td>At 6-mo TCD</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>15</td>
</tr>
<tr>
<td>Stenosis</td>
<td>7</td>
</tr>
<tr>
<td>Occlusion</td>
<td>14</td>
</tr>
</tbody>
</table>
occlusion. At 6 months, only 1 patient had experienced an MCA occlusion, 30 patients had an MCA stenosis, and 9 patients had a normalized MCA.

Progression/Regression According to Serial Changes

Among the 107 patients with initial MCA stenosis, 27 had a reestablished normal blood flow, 75 had persistent MCA stenosis, and 5 progressed to occlusion. Among the 36 patients with original MCA occlusion, 15 patients had a reestablished normal flow, 7 had a partially recanalized occlusion but with MCA stenosis, and 14 had a persistent occlusion (Figure 2).

By analyzing both the initial and repeated TCD findings, there were 42 patients (29%) in the normalized group, 88 patients (62%) in the stable group, and 13 patients (9%) in the progressed group (Table 3).

Univariate analyses showed that there were no significant differences among the 3 groups in the frequencies of vascular risk factors, including atrial fibrillation, relevant extracranial carotid tandem stenosis, and other conventional factors.

For the clinical events during the 6-month period, 18 (12.6%) of the patients had further documented vascular events, including 10 recurrent strokes (9 ischemic strokes and 1 hemorrhagic stroke), 5 TIAs, and 3 acute coronary syndromes.

For patients with atrial fibrillation, 3 patients with initially stenotic MCAs and 1 patient with an occluded MCA had normalized MCA flow at 6 months, and another 2 patients with an initially stenotic MCA had the same grade of stenosis. Only 1 patient with persistent MCA stenosis experienced a TIA. No patient was found to have an occluded MCA at the second TCD examination.

Relationship Between Clinical Events and Initial or 6-Month TCD Findings Alone

According to the initial TCD findings, further vascular events occurred in 14 (13%) of the patients with MCA stenosis and in 4 (11%) of the patients with MCA occlusion ($P=1.0$ by Fisher exact test). Similarly, if we categorized patients according to the results of the repeated TCD results at 6 months alone, there were no significant differences for the risk of further vascular events. At 6 months, there were 2 events (4.8%) among 42 patients with normal MCA, 12 events (14.6%) among 82 patients with MCA stenosis, and 4 events (21.1%) among 19 patients with MCA occlusion ($P=0.143$ by $\chi^2$ test).

Relationship Between Clinical Events and Serial Changes of TCD Findings

The most significant association with clinical events was found when the initial and repeated TCD findings were analyzed together. As shown in Table 3, 2 (4.8%) of the 42 patients in the normalized group, 11 (12.5%) of the 88 patients in the stable group, and 5 (38.5%) of the 13 patients in the progressed group had a vascular event ($\chi^2$ test, $P=0.006$) The increased risk of further vascular events in the progressed group remained significant after correction for sex, age, and other risk factors, such as diabetes, hypertension, ischemic heart disease, previous stroke or TIA, NIHSS of index stroke, and extracranial carotid artery status in a multiple logistic regression model (odds ratio 10.8, 95% CI 1.4 to 81.3; $P=0.02$). The only other significant factor was history of prior stroke or TIA (odds ratio 3.75, 95% CI 1.07 to 13.2; $P=0.04$). The causes of vascular events among these 3 groups are shown in Table 4.

Discussion

In the present study, repeated TCD examinations showed that the majority (71%) of the studied MCAs remained persistently abnormal. These findings are in contrast to the rapid

### Table 3. Changes of Occlusive MCA After 6 mo and Its Relationship With Further Vascular Events

<table>
<thead>
<tr>
<th>TCD Changes of Occlusive MCA After 6 mo</th>
<th>Further Vascular Events Within 6 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normalized artery</td>
<td>Yes, n (%) 40, No, n 42</td>
</tr>
<tr>
<td>Normalized flow from previous stenosis</td>
<td>2 (4.8) 63, 12</td>
</tr>
<tr>
<td>Normalized flow from previous occlusion</td>
<td>1 68</td>
</tr>
<tr>
<td>Stable artery</td>
<td>11 (12.5) 77, 88</td>
</tr>
<tr>
<td>Stenosis grading unchanged</td>
<td>6 53</td>
</tr>
<tr>
<td>Occlusion unchanged</td>
<td>2 12</td>
</tr>
<tr>
<td>Occlusion changed to stenosis</td>
<td>1 6</td>
</tr>
<tr>
<td>Stenosis downgraded</td>
<td>2 6</td>
</tr>
<tr>
<td>Progressed artery</td>
<td>5 (38.5) 8, 13</td>
</tr>
<tr>
<td>Stenosis upgraded</td>
<td>3 5</td>
</tr>
<tr>
<td>Stenosis changed to occlusion</td>
<td>2 3</td>
</tr>
<tr>
<td>Total</td>
<td>18 (12.6) 125, 143</td>
</tr>
</tbody>
</table>

By $\chi^2$ test, $P=0.0042$.

### Table 4. Relationship Between Pattern of MCA Changes and Further Clinical Events

<table>
<thead>
<tr>
<th>Pattern of MCA Changes</th>
<th>TIA</th>
<th>Ischemic Stroke</th>
<th>Hemorrhagic Stroke</th>
<th>Acute Coronary Syndromes</th>
<th>Total, N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normalized</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Stable</td>
<td>3</td>
<td>6</td>
<td>0</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Progressed</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>5</td>
<td>9</td>
<td>1</td>
<td>3</td>
<td>18</td>
</tr>
</tbody>
</table>
recanalization and normalization of MCA velocities that are noted if the occlusion is caused by embolization rather than in situ thrombus formation arising from preexisting MCA stenosis. This difference highlighted the dissimilarity of the underlying pathology between the Chinese and white populations. Nevertheless, in some patients, there was evidence of dynamic changes of MCA velocities. These findings of dynamic changes are consistent with previous reports of angiographic and ultrasound studies. However, in those reports, no relationships were reported between the progression of MCA lesions and clinical events.

Our data showed that progressed MCAs were associated with more subsequent vascular events after the index stroke. The events that were recorded probably occurred as the MCA progressed and were probably directly caused by that progression. This indicates that patients with progressed MCA occlusive disease could be at an increased risk of clinical cerebrovascular or cardiovascular events after stroke. Similar findings are well documented in patients with progression of coronary artery atherosclerosis. For cerebrovascular disease, previous studies also suggested that stroke recurrence, TIA, or myocardial infarction after a stroke reflects the progression of underlying vascular disease. It is important to point out that the second TCD in the present study was performed after the onset of a recurrent event, if any. Therefore, we consider the progression of the MCA lesion to serve as a marker of the progression of the generalized atherosclerosis process. Whether progression in MCA stenosis predicts vascular events requires further prospective study.

Our findings may have important clinical implications. If further prospective study confirms that the progression of MCA lesions predicts further vascular events, then periodic TCD examinations are justified to identify those patients at particularly high risk. For these high-risk patients, further study of more aggressive therapies, such as angioplasty, anticoagulation, or use of high-dose statin, should be considered.

There are limitations of the present study that merit discussion. First, there have been no validated criteria of MCA progression according to TCD. We used the only published criteria in the literature that categorize the severity of MCA stenosis by velocity. Second, we assumed a linear relationship between progressive luminal narrowing and rising flow velocities. However, an experimental study has shown that when stenosis reaches a critical severity, blood flow may also be compromised. The ensuing reduction in flow volume results in dampened velocity rather than increased velocity. Because of our sole reliance on velocities without study of the morphology of the arterial lumen, we may have misclassified progression or regression in the present study. Finally, we used the presence of diminished flow (<21% index) compared with flow in the contralateral MCA as an indicator of an occlusion. Despite this shortcoming, which should dilute the significance of our observation, the statistical analysis remains significant probably because of the relatively large number of patients studied.

In summary, progression of MCA occlusive disease is associated with further cerebrovascular or cardiovascular events among stroke patients with MCA lesions. More prospective studies are required to investigate the predictive value of serial TCD examinations in identifying patients with a high risk of further vascular events.

Acknowledgment
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References

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