Cerebral Microembolism in Patients With Retinal Ischemia

Christine A.C. Wijman, MD; Viken L. Babikian, MD; Ippolit C.A. Matjucha, MD; Behrooz Koleini, MD; Charles Hyde, MD; Michael R. Winter, MPH; Val E. Pochay

Background and Purpose—We investigated the frequency of cerebral microembolism detected by transcranial Doppler ultrasonography in patients with clinical evidence of retinal ischemia, including transient monocular blindness, central and branch retinal artery infarction, and ischemic oculopathy, and assessed its correlation with carotid artery stenosis.

Methods—Records of 331 consecutive patients examined during a 47-month period at the Neurovascular Laboratory were reviewed. Of the original 453 intracranial arteries, 186 middle cerebral arteries (MCAs) satisfied qualifying criteria that excluded patients with cardiac embolic sources. Forty-five MCAs ipsilateral to the symptomatic eye constituted the study group. The control group consisted of 141 asymptomatic MCAs. Microembolus detection studies were performed on transcranial Doppler instruments equipped with special software, and the degree of carotid artery stenosis was measured by cerebral or MR angiography or by color duplex studies.

Results—Microembolism was detected in 40.0% of study MCAs and 9.2% of controls (P<0.001). Microembolic signals were detected in 25.3% and 11.2%, respectively, of MCAs distal to carotid arteries (P<0.013). Severe (>70%) carotid stenosis or occlusion was more frequent in the study group (P<0.001). Microembolic signals were detected in 25.3% and 11.2%, respectively, of MCAs distal to carotid arteries with 70% to 100% and 0% to 69% stenosis (P=0.013).

Conclusions—In patients without cardiac embolic sources, cerebral microembolism is frequently present on the side of retinal ischemia, particularly during the week after onset of symptoms. It is often associated with severe stenosis or occlusion of the ipsilateral carotid artery. (Stroke. 1998;29:1139-1143.)

Key Words: cerebral embolism ■ retina ■ ultrasonography, Doppler

Transitory monocular blindness is recognized as a warning sign for retinal and cerebral infarction1–4 and is associated with ICA disease.5–7 Common mechanisms of TMB are embolism, causing transient occlusion of retinal arterioles, and retinal vascular insufficiency secondary to a hemodynamically significant stenosis of feeding arteries.8 Other less common etiologies include vasospasm, states of altered coagulability, and thrombocytosis.9 Since treatment strategies may be influenced by the mechanism of TMB, identification of the cause in an individual patient is of considerable clinical importance.

The notion of retinal embolism as an important cause of not only TMB but also of other forms of retinal ischemia, such as central or branch retinal artery occlusion, is predominantly based on clinical observations.10–13 In some patients, embolic material has been observed to course through retinal arterioles during episodes of transient monocular visual loss.10,11 However, retinal embolism tends to occur transiently and intermittently16 and thus cannot be excluded on clinical grounds alone.

Emboli that originate from ICA or more proximal vascular lesions can travel not only to the retina but also to cerebral branches of the ICA,11,17 and pathological evidence of cerebral emboli originating from ICA plaques has been demonstrated in this context.18 In addition, clinically undetectable cerebral embolism has been shown with cerebral angiography and indirectly with cerebral blood flow studies and electroencephalography in patients with transient retinal ischemia.19 However, these studies are not routinely obtained because of their invasiveness or lack of sensitivity. Therefore, the frequency of in vivo cerebral embolism in patients with retinal ischemia is presently unknown.

High-intensity transient signals detected by TCD have been identified in the intracranial vasculature of asymptomatic individuals as well as in patients with symptoms of cerebral ischemia associated with cardiac lesions20–22 or high-grade ICA stenoses.23–25 Laboratory models and pathological studies show that these signals can correspond to microemboli composed of thrombus, platelet-rich aggregates, atheromatous material, cholesterol, fat, and gaseous material.26,27 The ability to detect these signals provides a means to monitor cerebral microembolism in vivo.

In this study we investigated the frequency of cerebral microembolism in patients with clinical evidence of retinal ischemia.
ischemia, including TMB, central and branch retinal artery infarction, and ischemic oculopathy, and assessed its correlation with carotid artery stenosis.

**Subjects and Methods**

**Subjects**
The records of consecutive patients who were examined between March 29, 1993, and February 21, 1997, at the Neurovascular Laboratory of this tertiary care medical center were reviewed. During this time period, 453 intracranial arteries in 331 patients were examined for the presence of microembolic signals. Of these, all MCAs in patients with clinical evidence of ipsilateral retinal ischemia with or without associated symptoms of cerebral ischemia (n=51) and all asymptomatic MCAs (n=198) were selected for the purpose of this study. MCAs on the side of a recent carotid endarterectomy (n=10), arteries with incomplete data sheets or missing medical records (n=5), and arteries in patients with other concomitant cerebrovascular diagnoses (n=7) were excluded.

Clinical evidence of retinal ischemia included patients with TMB and patients with retinal infarction (central and branch retinal artery occlusion and ischemic oculopathy). TMB was defined as painless, transient, monocular visual loss, with complete resolution usually within minutes of symptom onset. Its diagnosis was clinically verified by one of the authors, a neurologist. Cases of central or branch retinal artery occlusion were confirmed by formal ophthalmologic examination. Chronic ocular ischemia was diagnosed in one patient, who had complete loss of vision ipsilateral to an occluded ICA with associated neovascular glaucoma, clouding of the cornea, and neovascularization of the iris. Patients with clinically silent retinal emboli were not included in this study.

Patients with evidence of cardioembolic disease were excluded from the study. All patients were routinely evaluated for the presence of cardioembolic disease by history, physical examination, and admission electrocardiograms; results of transthoracic or transesophageal echocardiograms were available in 23 patients with retinal ischemia and in 94 patients with asymptomatic MCAs. Six MCAs were excluded in the group of patients with retinal ischemia and 57 in the group of asymptomatic MCAs. Reasons for exclusion were atrial fibrillation (n=29), prosthetic heart valves (n=13), akinetic segments (n=11) or aneurysms (n=6) of the left ventricle, cardiac thrombi (n=2), recent myocardial infarction (n=1), and right-left shunts (n=1). The presence of aortic arch atheroma with debris was not considered a criterion for exclusion.

After patients with cardioembolic disease were excluded, the study group consisted of 45 MCAs in 44 patients with ipsilateral retinal ischemia. All patients had unilateral symptoms except for one patient who had episodes of TMB affecting one eye or the other at different times. Thirty MCAs were in patients with TMB alone, 7 in patients with TMB and transient ipsilateral hemispheric ischemia or infarction, 7 in patients with central or branch retinal artery occlusion, and 1 in a patient with ischemic oculopathy as described above. The 141 asymptomatic MCAs in 119 patients who had no symptoms of the ipsilateral retina or cerebral hemisphere and who had no cardioembolic lesions served as controls.

Antithrombotic medications prescribed during TCD testing were reviewed. In the group of symptomatic MCAs, 40 were in patients receiving antiplatelet agents or anticoagulants, 4 were in patients on no antithrombotic agents, and data were not available in 1 case. The corresponding figures for the asymptomatic group were 104, 34, and 3, respectively. An analysis of these data showed that the study sample was too small to determine the potential effects of these drugs on the prevalence of microembolic signals.

**Cerebrovascular Imaging Studies**
The presence of ICA disease proximal to the corresponding MCA was determined by cerebral angiography, duplex ultrasound, or MRA. An Ultramark 9-HDI instrument (Advanced Technology Laboratories) was used for duplex imaging, and a 1.5-T Sigma unit (General Electric Medical Systems) was used for MRI. The original films were reviewed to determine the degree of ICA stenosis. In patients with multiple imaging modalities, the cerebral angiogram was used whenever it was available, and the duplex ultrasound was preferred over the MRA. The degree of ICA stenosis was determined by contrast cerebral angiography in 63, duplex ultrasound in 101, and MRA in 18 arteries in the study. The distribution of these three imaging modalities was not different between the study and the control groups. Films were not available for review for seven arteries in the study group and 19 arteries in the control group, and the radiology reports were used instead. No imaging studies were obtained in four asymptomatic arteries. The methods of determining the degree of stenosis by contrast cerebral angiography and MRA have been described in an earlier report.21 The severity of stenosis by duplex ultrasound was based on the criteria of Faught et al.20 and Hood et al.21 The degree of extracranial ICA was divided into one of four categories: mild stenosis (0% to 29%), moderate stenosis (30% to 69%), severe stenosis (70% to 99%), and occlusion.

**Statistical Methods**
All data were stored on a personal computer with the use of Microsoft Excel software (version 5.0). Group comparisons were made with the χ² test, Fisher’s exact test (two-tailed), or the Wilcoxon rank sum test. Adjusted group comparisons were made with the Mantel-Haenszel χ² test. All statistical analyses were performed at the Data Coordinating Center of the Boston University School of Public Health with the use of the SAS System for Windows, Release 6.12.

**Results**
The mean ages of the study and control populations were 70.0 years (range, 51 to 91 years) and 67.1 years (range, 30 to 91 years), respectively. Age distribution was not significantly different between the two groups. All MCAs in the study group were from male patients, as were all but four MCAs in the control group.

Microembolic signals were detected in 40.0% of MCAs in the study group and in 9.2% of MCAs in the control group. The difference between the two groups was significant (Table 1). In the subgroup of patients with TMB (with or without associated cerebral ischemia), microembolic signals were detected in 16 of 37 MCAs (43.2%). Again, there was a significant difference with the asymptomatic group (P<0.001; OR, 7.5; 95% CI, 3.2 to 17.8).

The median time interval between onset of symptoms and TCD testing was 9 days (range, 0.16 to 250 days). Microem-
bolic signals occurred in 13 of 21 study group MCAs (61.9%) that were tested within a week from symptom onset (Table 1) and in only 5 of 24 MCAs (20.8%) that were tested more than a week after the onset of symptoms. The difference between the two groups was significant ($P < 0.005$; OR, 6.2; 95% CI, 1.6 to 23.1).

Twelve of the patients in the study group with microembolic signals underwent microembolic detection studies of both MCAs, one on the side of the symptomatic eye, and one on the asymptomatic side. Of these, 10 (83.3%) had microembolic signals only in the MCA ipsilateral to the symptomatic eye, 1 (8.3%) in both MCAs, and 1 (8.3%) in only the asymptomatic MCA. Thus, when present, microembolic signals usually occurred only on the side of the symptomatic eye.

The incidence of microembolic signals correlated with the degree of ICA stenosis proximal to the corresponding MCA. Microembolic signals occurred in 19 of 75 MCAs (25.3%) distal to ICAs with luminal stenosis of 70% or more and in only 12 of 107 MCAs (11.2%) distal to ICAs with luminal stenosis of 69% or less ($P < 0.013$; OR, 2.7; 95% CI, 1.2 to 5.9). (Note that $n = 182$ because there are no data available on the severity of ICA stenosis for four MCAs in the control group.)

Severe ICA stenosis occurred more frequently in the study group than in the control group (Table 2). Severe ICA stenosis or occlusion was present proximal to 33 of 45 MCAs (73.3%) in the study group and 42 of 137 MCAs (30.7%) in the control group ($P < 0.001$; OR, 6.2; 95% CI, 2.9 to 13.2).

ICA stenosis of less than 30% was observed in five study group patients, three without and two with microembolic signals in the MCA ipsilateral to the symptomatic retina. Transesophageal echocardiography showed moderate to severe aortic arch plaques exceeding 5-mm thickness in the latter two patients.

Because of the significant correlation between the frequency of microembolic signals and the degree of ICA stenosis and the higher frequency of severe ICA stenosis in the study group, the interaction between these variables was analyzed further. After we controlled for the degree of ICA stenosis, the MCAs in the study group were still five times more likely to have microembolic signals than the MCAs in the control group ($P < 0.001$; OR, 5.0; 95% CI, 2.2 to 11.4).

### Table 1. Frequency of Microembolic Signals in MCAs of Patients With Ipsilateral Retinal Ischemia and in Asymptomatic MCAs

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Frequency of Microembolic Signals</th>
<th>$P$</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCAs in patients with ipsilateral retinal ischemia</td>
<td>18/45 (40.0%)</td>
<td>$&lt;0.001$</td>
<td>6.6</td>
<td>2.9–15.0</td>
</tr>
<tr>
<td>MCAs in patients with ipsilateral retinal ischemia tested $\leq 7$ days</td>
<td>13/21 (61.9%)</td>
<td>$&lt;0.001$</td>
<td>16.0</td>
<td>5.6–45.7</td>
</tr>
<tr>
<td>Asymptomatic MCAs</td>
<td>13/141 (9.2%)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

### Table 2. Degree of ICA Stenosis Proximal to MCAs of Patients With Ipsilateral Retinal Ischemia and Asymptomatic MCAs

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Mild (0–29%)</th>
<th>Moderate (30–69%)</th>
<th>Severe (70–99%)</th>
<th>Occluded (100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICAs in patients with ipsilateral retinal ischemia</td>
<td>5/45</td>
<td>7/45</td>
<td>27/45</td>
<td>6/45</td>
</tr>
<tr>
<td>ICAs proximal to asymptomatic MCAs</td>
<td>45/137</td>
<td>50/137</td>
<td>36/137</td>
<td>6/137</td>
</tr>
</tbody>
</table>

Discussion

In this study we determined the frequency of in vivo cerebral microembolism in patients with retinal ischemia. Microembolic signals were detected in 40% of MCAs in patients with ipsilateral symptoms of retinal ischemia and in 62% of those tested within a week from symptom onset. These rates are more than four and six times as high, respectively, as the rate of cerebral microembolism in the asymptomatic controls. In addition, microembolic signals were usually detected only on the side of the symptomatic eye, indicating that symptoms of retinal ischemia coincide with the presence of cerebral microembolism. Despite this high frequency of cerebral microembolism in the study group, it is likely that we underestimated the true frequency of cerebral microembolism. Half-hour microembolic signal detection studies may be too short to identify all patients with cerebral microembolism. Furthermore, the frequency of microembolic signals peaks between 4 and 6 AM, a test period that is outside the regular hours of our laboratory. In addition, although the microembolic signal criteria that we used were similar to those established by the Consensus Committee, “small” particles less than 9 dB in intensity were excluded, possibly resulting in an underestimation of the true frequency of microembolism. Nevertheless, our findings support the
Cerebral Microembolism in Retinal Ischemia

notion of an embolic etiology\textsuperscript{13} in the majority of cases with retinal ischemia. Embolism may either be the sole or one of several causal factors.

Retinal ischemia is associated with ICA disease.\textsuperscript{5,2} In this study a high-grade ICA stenosis of 70% or more, or occlusion, was detected in 73% of cases with retinal ischemia. The frequency of cerebral microembolism correlated significantly with the severity of ICA stenosis, suggesting that the source of the microemboli was often the ipsilateral carotid artery. However, after we controlled for the degree of ICA stenosis, microembolism was still five times more likely to occur in the arteries of symptomatic patients, indicating that additional factors contributed to the association of cerebral microembolism with retinal ischemia. One of these factors might be the level of activity of the ongoing process in the vascular wall. It is of interest that embolism to the retina may arise from embolic sources other than the ICA. Two patients with cerebral microembolism and without ICA stenosis had severe atheromatous aortic arch plaques.

The majority of our patients with retinal ischemia and cerebral microembolism did not have symptoms of cerebral ischemia, nor did the cases with cerebral microembolism in the asymptomatic control group. These microemboli were “silent” in that they did not result in clinically detectable neurological deficits. Indirect evidence of clinically undetectable cerebral involvement in patients with retinal ischemia has been reported previously,\textsuperscript{12} and pathological studies have shown incidental emboli in the lumen of cerebral arterioles without evidence of ischemic changes in the adjacent brain tissue.\textsuperscript{34,35} In addition, silent retinal embolism is frequently detected by routine funduscopic examination in patients without clinical evidence of retinal ischemia.\textsuperscript{15,36} Thus, asymptomatic retinal and cerebral emboli occur and do not always precede clinically or radiologically evidenced ischemia or infarction. Conversely, longitudinal follow-up studies suggest that retinal emboli as detected on funduscopic examination\textsuperscript{2,15} and cerebral microemboli\textsuperscript{26} as detected by TCD are both associated with an increased risk for subsequent cerebral infarction. However, the magnitude of this risk is presently unknown.

This study has several limitations. First, the patient population consisted predominantly of elderly white men, many with multiple risk factors for cerebrovascular disease referred to a tertiary care medical center. The relevance of our findings to an unselected population should be interpreted in this context. Other mechanisms of retinal ischemia may occur more frequently in different patient populations. Second, data were collected retrospectively and should be interpreted within the limits of such a study design. Third, the effects of antiplatelet agents and anticoagulant drugs on cerebral microembolism remain undetermined and may have affected the study’s results. Lastly, various imaging modalities were used to determine the severity of ICA stenosis, thereby introducing a certain degree of inconsistency in the methods.

In summary, in patients without cardioembolic sources, cerebral microembolism is frequently present on the side of retinal ischemia, particularly during the week after onset of symptoms. It is often associated with severe stenosis or occlusion of the ipsilateral ICA.

References

Cerebral Microembolism in Patients With Retinal Ischemia
Christine A. C. Wijman, Viken L. Babikian, Ippolit C. A. Matjucha, Behrooz Koleini, Charles Hyde, Michael R. Winter and Val E. Pochay

Stroke. 1998;29:1139-1143
doi: 10.1161/01.STR.29.6.1139

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/29/6/1139