Intraoperative Microemboli and Low Middle Cerebral Artery Blood Flow Velocity Are Additive in Predicting Development of Cerebral Ischemic Events After Carotid Endarterectomy

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Background and Purpose—Microemboli generated during dissection of the carotid arteries in patients undergoing carotid endarterectomy result in postoperative cerebral ischemic events. The purpose of this study was to determine whether these events correlate with middle cerebral artery blood flow velocity.

Methods—One hundred sixty-three patients with ipsilateral internal carotid artery stenosis (>70%) underwent carotid endarterectomy under transcranial Doppler monitoring of mean blood flow velocity and microembolic signals in the ipsilateral middle cerebral artery.

Results—Logistic regression analysis of several variables demonstrated that only middle cerebral artery mean blood flow velocity during carotid dissection was significantly associated with new postoperative neurological deficits in patients with microembolic signals during carotid dissection (95% CI, 1.069 to 1.528; \(P=0.0072\)). The combination of low middle cerebral artery mean blood flow velocity (\(<28\) cm/s) and microembolic signals \(>10\) during carotid dissection resulted in improved specificity and positive predictive value for the development of new postoperative neurological deficits when compared with either criterion used alone.

Conclusions—Intraoperative microemboli and low middle cerebral artery mean blood flow velocity are additive in predicting the development of cerebral ischemic events after carotid endarterectomy. (Stroke. 2008;39:3088-3091.)

Key Words: carotid endarterectomy • diffusion-weighted imaging • flow velocity • microemboli • transcranial Doppler ultrasonography

Hemispheric cerebral hypoperfusion during internal carotid artery (ICA) clamping and intraoperative generation of emboli from the surgical site play a significant role in the development of new neurological deficits such as transient ischemic attacks or stroke immediately after carotid endarterectomy (CEA). These deficits may also occur secondary to postoperative generation of emboli from the surgical site. Intraoperative assessment of the middle cerebral artery (MCA) with transcranial Doppler (TCD) allows online surveillance of hemodynamic changes and can detect passage of cerebral microemboli.

Microembolic signals (MES) on intraoperative TCD monitoring are detected in more than 90% of patients undergoing CEA. The number of detectable MES varies according to the different stages of CEA. Although the highest number of MES occurs during declamping of the ICA, detection of MES during dissection of the carotid arteries or during the first postoperative hour correlates with the development of new ischemic lesions on postoperative diffusion-weighted MRI (DWI) or new neurological deficits immediately after CEA. The target vessel is not opened during dissection, and, thus, all detectable MES are solid. Furthermore, during this stage of the procedure, the fragile plaque, a source of emboli, has not yet been removed and is still exposed to blood flow. Detectable MES during the early postoperative period may also be solid (eg, thromboemboli). In addition, an MES count \(>10\) during these phases is a predictor of the development of new neurological deficits. By contrast, a high number of harmless gaseous MES may develop during carotid declamping.

Caplan and Hennerici previously reported that hemodynamic and embolic mechanisms are strictly linked and may interact to determine the ultimate degree of cerebral ischemia. According to their concept, low blood flow velocity in the cerebral artery may impair clearance of emboli generated from a proximal lesion, which subsequently facilitates the onset of ischemia due to emboli in poorly perfused areas of the brain. In CEA, MCA blood flow velocity may be lower...
during dissection of the carotid arteries than during the early postoperative period. However, the interplay between MCA blood flow velocity and significant MES count during dissection of the carotid arteries has not been examined.

The purpose of the present study was to determine whether cerebral ischemic events that are associated with microemboli during dissection of the carotid arteries in CEA correlate with MCA blood flow velocity.

### Subjects and Methods

#### Patient Selection

Over a period of 7 years, 220 consecutive patients with ipsilateral ICA stenosis (≥70%) underwent CEA of the carotid bifurcation at our institution. Of these patients, 3 patients underwent urgent CEA for progressing stroke or crescendo transient ischemic attacks. Furthermore, 25 patients without reliable TCD monitoring due to failure to obtain an adequate bone window and 29 patients with MCA mean blood flow velocity during ICA clamping of <40% of the preclamp value for more than 5 minutes were excluded from the present study. Thus, a total of 163 patients were enrolled in the present study.

#### Carotid Endarterectomy

All patients underwent surgery under general anesthesia. An intraluminal shunt was not used in these procedures.

#### Transcranial Doppler Monitoring

TCD was performed using a PIONEER TC2020 (EME; software version 2.50, 2-MHz probe, 1.5 cm diameter, insonation depth 40 to 66 mm, scale −100 and +150 cm/s, sample volume 2 mm, 64-point fast Fourier transform, fast Fourier transform length 2 mm, fast Fourier transform overlap 60%, high-pass filter 100 Hz, detection threshold 9 dB, minimum increase time 10 ms). TCD data were stored on a hard disk using a coding system and were later analyzed manually by an investigator who was blind to patient information.

MES were identified during carotid dissection (from skin incision until ICA clamping) according to the recommended guidelines, and patient groups were analyzed according to those with MES ≥10 and <10. Mean blood flow velocity (MFV) values were defined as diastolic flow velocity + one third (systolic flow velocity minus diastolic flow velocity; cm/s). The MFV measured at the start of skin incision was defined as MFV during carotid dissection.

#### MRI

DWI was performed using a 1.5-Tesla whole body imaging system (Signa MR/i, GE Healthcare, Milwaukee, Wis) within 3 days before and 24 hours after surgery. A neuroradiologist who was blinded to the patients’ clinical information analyzed the MRIs.

### Assessment of Neurological Deficits

All patients were neurologically tested immediately before induction of general anesthesia, at recovery from general anesthesia, and at 24 hours after surgery by a neurologist who was blinded to the patients’ TCD information.

### Statistical Analysis

Data are expressed as the mean±SD. In the subgroup of patients with at least one MES during carotid dissection, the relationship between each variable and the development of new postoperative ischemic lesions on DWI or new postoperative neurological deficits such as transient ischemic attacks or stroke was evaluated with univariate analysis using the Mann-Whitney’s U test or χ² test. A multivariate statistical analysis of factors related to development of new postoperative ischemic lesions on DWI or new postoperative neurological deficits in the subgroup of patients with at least one MES during carotid dissection was also performed using a logistic regression model. Variables with P<0.2 in the univariate analyses were selected for analysis in the final model. Differences were deemed statistically significant if P<0.05. In addition, the accuracy of the MES number and MCA MFV in predicting the development of new postoperative ischemic lesions on DWI or new postoperative neurological deficits was assessed using receiver operating characteristic curves. The receiver operating characteristic curves of MES and MCA MFV were calculated in increments of one number and 1 cm/s, respectively.

### Results

Of 163 patients studied, 154 patients were men and 9 were women. Mean age of the patient population was 68.6±6.5 years (mean±SD) ranging from 47 to 81 years. Concomitant disease states and symptoms were recorded, including 126 patients with hypertension, 54 patients with diabetes mellitus, and 62 patients with hyperlipidemia. One hundred eighteen patients evinced ipsilateral carotid territory symptoms within 6 months before surgery, including 35 patients with transient ischemic attacks, 22 patients with transient ischemic attacks and subsequent stroke, and 61 patients with stroke alone. Forty-five patients had asymptomatic ICA stenosis.

Patients underwent neurological assessment at 31±11 minutes after completing skin closure. Eight patients (4.9%) developed new postoperative neurological deficits. All the deficits included hemiparesis contralateral to CEA.

### Table 1. Univariate Analysis of Factors Related to the Development of New Postoperative Ischemic Lesions on DWI or Postoperative New Neurological Deficits in the Subgroup of Patients With MES During Carotid Dissection

<table>
<thead>
<tr>
<th>Variables</th>
<th>New Postoperative Ischemic Lesions on DWI</th>
<th>New Postoperative Neurological Deficits</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n=23)</td>
<td>No (n=29)</td>
</tr>
<tr>
<td>Age, years (mean±SD)</td>
<td>70.2±6.2</td>
<td>66.7±7.0</td>
</tr>
<tr>
<td>Male gender</td>
<td>23 (100%)</td>
<td>27 (93%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>19 (83%)</td>
<td>25 (86%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>11 (48%)</td>
<td>8 (28%)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>6 (26%)</td>
<td>11 (38%)</td>
</tr>
<tr>
<td>Symptomatic lesion</td>
<td>19 (83%)</td>
<td>23 (79%)</td>
</tr>
<tr>
<td>MES ≥10 during carotid dissection</td>
<td>10 (43%)</td>
<td>4 (14%)</td>
</tr>
<tr>
<td>MCA MFV during carotid dissection, cm/s</td>
<td>26±6</td>
<td>41±9</td>
</tr>
</tbody>
</table>

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deficits resolved completely within 12 hours in 6 patients. However, the neurological deficits in the remaining 2 patients remained at 24 hours after surgery. New postoperative ischemic lesions in the cerebral hemisphere ipsilateral to CEA on DWI developed in 28 patients (17.2%), a single spotty lesion in 10 patients and multiple spotty lesions in 18 patients; the lesions were located in the border zones in 12 patients, in the cerebral cortex in 4 patients, and in both areas in 12 patients.

At least one MES and MES ≥10 were detected in 52 patients (31.9%) and 14 patients (8.6%) during carotid dissection, respectively. In 23 of the 28 patients with new postoperative ischemic lesions in the cerebral hemisphere ipsilateral to CEA on DWI, at least one MES occurred during carotid dissection. All 8 patients with new postoperative neurological deficits exhibited at least one MES during carotid dissection and new postoperative ischemic lesions on DWI.

In 52 patients with at least one MES during carotid dissection, patients with new postoperative ischemic lesions on DWI were significantly older than those without, and the incidence of MES ≥10 during carotid dissection was significantly higher in patients with new postoperative ischemic lesions on DWI or new postoperative neurological deficits than in those without (Table 1). Furthermore, the MFV during carotid dissection was significantly lower in patients with new postoperative ischemic lesions on DWI or new postoperative neurological deficits than in those without (Table 1). Multivariate analysis revealed that only MFV during carotid dissection was significantly associated with the development of new postoperative ischemic lesions on DWI (95% CI, 1.208 to 3.408; \( P = 0.0075 \)) or new postoperative neurological deficits (95% CI, 1.069 to 1.528; \( P = 0.0072 \)).

The relationship among the number of MES, MCA MFV during carotid dissection, development of new postoperative ischemic lesions on DWI, and new postoperative neurological deficits is shown in the Figure. Sensitivity, specificity, positive predictive value, and negative predictive value in the cutoff point lying closest to the left upper corner of the receiver operating characteristic curve for the prediction of new postoperative ischemic lesions on DWI or new postoperative neurological deficits are also shown in Table 2. Among patients with at least one MES during carotid dissection, a low MCA MFV (≤35 cm/s) was more sensitive than MES ≥10 with a moderately better positive predictive value for new postoperative ischemic lesions on DWI. Furthermore, the combination of low MCA MFV (≤35 cm/s for new postoperative ischemic lesions on DWI or ≤28 cm/s for new postoperative neurological deficits) and MES ≥10 greatly improved the specificity and positive predictive value when compared with either criterion alone. Conversely, the combination of MCA MFV >35 cm/s or >28 cm/s and MES <10 identified development of new postoperative ischemic lesions on DWI or new postoperative neurological deficits, respectively, with a sensitivity and positive predictive value of zero.

### Discussion

Spencer showed that patients with an MCA flow velocity during ICA clamping of less than 40% of the preclamp value were at higher risk of developing new postoperative neurological deficits secondary to hemispheric hypoperfusion.\(^4\) The present study investigated development of cerebral ischemic lesions or events secondary to MES rather than hemispheric hypoperfusion during ICA. Thus, patients with an MCA

**Table 2. Prediction of New Postoperative Ischemic Lesions on DWI or Postoperative New Neurological Deficits in the Subgroup of Patients With at Least One MES During Carotid Dissection**

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MES ≥10 only</td>
<td>43%</td>
<td>86%</td>
<td>71%</td>
<td>66%</td>
<td>63%</td>
<td>80%</td>
<td>36%</td>
<td>92%</td>
</tr>
<tr>
<td>MCA MFV ≤35 or 28 cm/s* only</td>
<td>91%</td>
<td>83%</td>
<td>81%</td>
<td>92%</td>
<td>88%</td>
<td>70%</td>
<td>35%</td>
<td>97%</td>
</tr>
<tr>
<td>MES ≥10 and MCA MFV ≤35 or 28 cm/s*</td>
<td>35%</td>
<td>100%</td>
<td>100%</td>
<td>66%</td>
<td>50%</td>
<td>98%</td>
<td>80%</td>
<td>91%</td>
</tr>
<tr>
<td>MES ≤10 only</td>
<td>57%</td>
<td>14%</td>
<td>34%</td>
<td>29%</td>
<td>37%</td>
<td>20%</td>
<td>8%</td>
<td>64%</td>
</tr>
<tr>
<td>MCA MFV &gt;35 or 28 cm/s only*</td>
<td>9%</td>
<td>17%</td>
<td>8%</td>
<td>19%</td>
<td>12%</td>
<td>30%</td>
<td>3%</td>
<td>65%</td>
</tr>
<tr>
<td>MES &lt;10 and MCA MFV &gt;35 or 28 cm/s*</td>
<td>0%</td>
<td>31%</td>
<td>0%</td>
<td>28%</td>
<td>0%</td>
<td>55%</td>
<td>0%</td>
<td>75%</td>
</tr>
</tbody>
</table>

* A total of 35.0 cm/s for new postoperative ischemic lesions on DWI or 28.0 cm/s for new postoperative neurological deficits.
velocity during ICA clamping of less than 40% of the preclamp value were excluded from the present study.

Orlandi et al recently performed TCD monitoring during carotid artery stenting and also demonstrated that MCA median blood flow velocity values at the start of the procedure were significantly lower in patients with new postoperative neurological deficits than in those without. The results of our multivariate analysis correspond with this finding and support the concept proposed by Caplan and Hennerici. In the present study, among patients with at least one MES during carotid dissection, MCA MFV was better than the number of MES in terms of predicting new postoperative ischemic lesions on DWI. This supports the result of multivariate analysis. Furthermore, the combination of MCA MFV (cutoff point = 35 cm/s for new postoperative ischemic lesions on DWI or 28 cm/s for new postoperative neurological deficits) and number of MES (cutoff point = 10) was a more powerful predictor of development or absence of new postoperative neurological deficits when compared with either criterion alone.

Several investigators have demonstrated that high numbers of MES detected during the first postoperative hour are significantly associated with development of new postoperative neurological deficits. Thus, although postoperative TCD monitoring was not performed, postoperative MES may affect the experimental results observed in the present study.

In conclusion, intraoperative microemboli and low MCA MFV are additive in predicting the development of cerebral ischemic events after CEA. This conclusion raises further research questions in regard to interventions to reduce the risk of perioperative ischemic complications such as prevention of embolus formation and/or avoidance of low MFV. In addition, if the intervention is implemented on the basis of MCA MFV and MES number, it is unlikely that patients at low risk of ischemic complications will be unnecessarily exposed to the intervention, whereas those at high risk of the ischemic complications will have the opportunity to benefit from the intervention.

Disclosures

None.

References

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