Preoperative single-slab 3D time-of-flight magnetic resonance angiography predicts development of new cerebral ischemic events after carotid endarterectomy

Clinical article

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Object. Preoperative impairment of cerebral hemodynamics predicts the development of new cerebral ischemic events after carotid endarterectomy (CEA), including neurological deficits and cerebral ischemic lesions on diffusion weighted MR imaging. Furthermore, the signal intensity of the middle cerebral artery (MCA) on single-slab 3D time-of-flight MR angiography (MRA) can assess hemodynamic impairment in the cerebral hemisphere. The purpose of the present study was to determine whether, on preoperative MR angiography, the signal intensity of the MCA can be used to identify patients at risk for development of cerebral ischemic events after CEA.

Methods. The signal intensity of the MCA ipsilateral to CEA on preoperative MR angiography was graded according to the ability to visualize the MCA in 106 patients with unilateral internal carotid artery stenosis (≥70%). Diffusion weighted MR imaging was performed within 3 days of and 24 hours after surgery. The presence or absence of new postoperative neurological deficits was also evaluated.

Results. Cerebral ischemic events after CEA were observed in 16 patients. Reduced signal intensity of the MCA on preoperative MR angiography was the only significant independent predictor of postoperative cerebral ischemic events. When the reduced MCA signal intensity on preoperative MR angiography was defined as an impairment in cerebral hemodynamics, MR angiography grading resulted in an 88% sensitivity and 63% specificity, with a 30% positive- and a 97% negative-predictive value for the development of postoperative cerebral ischemic events.

Conclusions. Signal intensity of the MCA on preoperative single-slab 3D time-of-flight MR angiography is useful for identifying patients at risk for cerebral ischemic events after CEA. (DOI: 10.3171/2009.2.JNS081233)

Key Words • carotid endarterectomy • cerebral ischemic event • magnetic resonance angiography

Neurological deficits after CEA are uncommon, occurring in < 5% of patients. Hemodynamic cerebral ischemia due to hemispheric hypoperfusion during ICA clamping and the generation of emboli from the surgical site play significant roles in the development of new cerebral ischemic events after CEA, including new neurological deficits and new cerebral ischemic lesions on diffusion weighted MR imaging.15,24,25 Several investigators have demonstrated that preoperative impairment of cerebral hemodynamics predicts the development of new postoperative cerebral ischemic lesions on diffusion weighted MR imaging related to the generation of microemboli during CEA2 as well as new postoperative neurological deficits due to hemispheric hypoperfusion during ICA clamping.12

Three-dimensional TOF MR angiography uses signals generated by the inflow of fresh, unsaturated, and fully magnetized blood-spins into the imaged slab.5,14 These spins are gradually saturated during movement within the slab, which causes signal loss in the peripheral arteries. The signal loss due to the saturation effect depends on the flow velocity—that is, it is more pronounced

Abbreviations used in this paper: CEA = carotid endarterectomy; ICA = internal carotid artery; MCA = middle cerebral artery; TOF = time-of-flight.
with lower flow velocity, particularly in single-slab 3D TOF MR angiography. By contrast, hemodynamics in the cerebral hemisphere correlate with blood flow velocity of the ipsilateral MCA. Furthermore, one study reported that the signal intensity of the MCA on single-slab 3D TOF MR angiography can be used to assess hemodynamic impairment in the cerebral hemispheres with ICA stenoocclusive diseases.

The purpose of the present study was to determine whether signal intensity of the MCA on preoperative single-slab 3D TOF MR angiography can identify patients at risk for development of new cerebral ischemic events after CEA.

**Methods**

**Patient Population**

One-hundred six patients with ipsilateral ICA stenosis (≥70%) and useful residual function (modified Rankin Disability Scale score of 0, 1, or 2) who underwent CEA between January 2006 and August 2008 were enrolled in the present study. One hundred three of the 106 patients were men and 3 were women. The mean age of the patient population was 68.9 ± 6.2 years (± SD; range 47–81 years). None of the patients had an altered level of consciousness, restlessness, dementia, or cardiac failure. Seventy-eight patients had ipsilateral carotid territory symptoms, 22 patients had transient ischemic attacks, 19 patients had transient ischemic attacks and subsequent stroke, and 37 patients had stroke alone. An additional 28 patients exhibited asymptomatic ICA stenosis.

All patients underwent preoperative MR angiography in the cervical portion of the carotid artery. The overall mean degree of ICA stenosis was 86.8 ± 8.7% (range 70–99%) as per the North American Symptomatic Carotid Endarterectomy Trial. Twenty-five patient had stenosis >70% or occlusion in the contralateral ICA.

This study was reviewed and approved by the institutional ethics committee of our university. Written informed consent was obtained from all patients or their next of kin.

**Intraoperative Management**

Patients received midazolam (7.5 mg orally) preoperatively. We performed CEA after induction of general anesthesia. Anesthesia was induced with fentanyl (2–3 µg/kg intravenously), propofol (1.5–3 mg/kg intravenously), and vecuronium (0.1 mg/kg intravenously) and was maintained by repeated boluses of fentanyl (1–2 µg/kg intravenously), vecuronium, and 0.4–1.0% inspired isoflurane. Artificial ventilation with an air-oxygen mixture (inspired fraction of oxygen ~0.30) was performed in all cases. Analysis of intermittent drawn arterial blood gas samples ensured normoventilation (4.7–5.2 kPa). Routine monitoring during anesthesia included standard electrocardiography, an intraarterial catheter for direct arterial blood pressure measurement, pulse oximetry, and capnography. Blood pressure was kept stable in a range of ±20% of the preoperative level throughout the procedure by adjusting the depth of anesthesia or, if needed, by intravenous administration of a vasodilator (nitroglycerin) or a vasoconstrictor (theodrenaline).

Neither an intraluminal shunt nor a patch graft was used in these procedures. A bolus of heparin (5000 U) was given prior to ICA clamping. The mean duration of ICA clamping was 36 minutes (range 22–46 minutes).

**Magnetic Resonance Imaging**

The MR angiography study was performed as described previously using a 3.0-T imager (Signa Excite HD, GE Healthcare). Axial single-slab 3D TOF MR angiograms of the cervical portion of the carotid artery were obtained at the carotid bifurcation by using 5-in surface coils (TR 21; TE 3; variable flip angle 17–34° in the inferosuperior direction; matrix size 512 × 256; FOV 22 cm; slice thickness 1.2 mm; partition size 60 with zero-fill interpolation [120 slices with 0.6-mm intervals]; number of excitations 1; presaturation pulse above the slab, a fat suppression pulse, and a flow compensation; and acquisition time 4 minutes 26 seconds). An axial single-slab 3D TOF MR angiography of the intracranial arteries, which was parallel to the anterior-commissure-posterior-commissure line and was covered from the pontomedullary junction to the corpus callosum, was obtained using an eight-channel head coil (TR 30; TE 3.7; variable flip angles of 17–34° in the inferosuperior direction; matrix size 512 × 320; FOV 24 cm; slice thickness 1.0 mm; partition size 90 with zero-fill interpolation [180 slices with 0.5 mm intervals]; number of excitations 1; magnetization transfer pulse and flow compensation; and acquisition time 262 seconds).

The signal intensity of the MCA on the intracranial MR angiograms was visually classified into the following 4 grades according to one’s ability to visualize the MCA (Fig. 1): all M1 branches of the MCA could be visualized to the cortical surface (Grade A); one or more M1 branches could not be visualized on the cortical surface (Grade B); one or more M1 branches could not be visualized along its course (Grade C); the M1 could not be visualized along its course (Grade D).

Diffusion weighted MR imaging was performed using a 1.5-T whole-body system (Signa MR/I, GE Healthcare) within 3 days of and 24 hours after surgery. The images were acquired using a single-shot, spin echo, echo planar imaging pulse sequence with (TR 10,000 msec; TE 97 msec; 1 excitation, FOV 22 × 22 cm, matrix 128 × 128, 3 orthogonal motion probing gradients with a b value of 1000 seconds/mm²; Imaging time was 40 seconds for acquisition of 20 sections with thickness of 5 mm and no interslice gaps covering from the vertex to the cerebellum. Isotropic diffusion weighted images were calculated by averaging 3 anisotropic images with gradients of the x, y, or z direction.

A neuroradiologist (M.S.), who was blinded to the patients’ clinical information and MR angiography grades, was asked to determine whether new postoperative ischemic lesions were present on diffusion weighted MR images.

**Assessment of Neurological Deficits**

All patients underwent neurological testing, conduct-
ed by a neurologist who was blinded to the patients’ clinical information, immediately before induction of general anesthesia and after recovery from general anesthesia. The presence or absence of new postoperative neurological deficits was recorded at this time.

Statistical Analysis

Descriptive statistics were expressed as the mean ± SD. The incidence of new postoperative cerebral ischemic events (neurological deficits and/or cerebral ischemic lesions on diffusion weighted MR imaging) among the 4 MR angiography grade groups was evaluated using the chi-square test followed by Bonferroni inequality. Differences between each MR angiography grading group were deemed statistically significant if probability values were < 0.05/6 = 0.0083. The relationship between each variable and the development of new postoperative cerebral ischemic events was evaluated with univariate analysis using the Mann-Whitney U-test or chi-square-test. A multivariate statistical analysis of factors related to development of new postoperative cerebral ischemic events was also performed using a logistic regression model. Variables with probability values < 0.2 in the univariate analyses were selected for analysis in the final model. In these analyses, MR angiography Grade A was defined as normal signal intensity of the MCA and Grades B, C, and D were defined as reduced signal intensity of the MCA. Differences were deemed statistically significant if probability values were < 0.05.

Results

Of 106 patients studied, signal intensity in 59, 25, 15 and 7 was preoperatively classified as MR angiography Grade A, B, C and D, respectively.

Diffusion weighted MR imaging in 14 patients (13%) showed new postoperative ischemic lesions in the cerebral hemisphere ipsilateral to the site of CEA. All the new ischemic lesions were spotty, with diameters ≤ 1.5 cm. New postoperative neurological deficits developed in 5 patients (5%); 3 (3%) with new postoperative cerebral ischemic lesions on diffusion weighted MR imaging and 2 (2%) without. While postoperative neurological deficits resolved completely within 12 hours in 3 of 5 patients, the neurological deficits in the remaining 2 persisted for more than 24 hours after surgery. Thus, a total of 16 patients experienced new postoperative ischemic events (postoperative cerebral ischemic lesions on diffusion weighted MR imaging and/or postoperative neurological deficits).

The number and incidence of new postoperative cerebral ischemic events in patients with each MR angiography grade are shown in Fig. 2. While the incidence was significantly higher in patients with Grade B or C signal than in those with Grade A signal, there were not differences in the incidences of new postoperative cerebral ischemic events when comparing between other MR angiography grades.

The results of univariate analysis of factors related to the development of postoperative cerebral ischemic events are summarized in Table 1. The degree of ICA stenosis and the incidence of reduced signal intensity of the MCA were significantly higher in patients with new postoperative cerebral ischemic events than in those without. Other variables were not significantly associated with the development of postoperative cerebral ischemic events. After eliminating variables that were closely related to others, the following items (with p < 0.2 detected on the univari-

![Fig. 1. The degree of visualization of the ipsilateral MCA on MR angiograms was graded as follows: all M3 branches of the left MCA are visualized on the cortical surface (Grade A); one M3 branch is not on to the cortical surface (Grade B, arrow); one M2 branch is not visualized along its course (Grade C, arrow); and the M1 is not visualized along its course (Grade D, arrow).]

![Fig. 2. Graph demonstrating the number and incidence of new postoperative cerebral ischemic events among the 4 MR angiography (MRA) grades.]

![Table 1. The number of new postoperative ischemic events among the 4 MR angiography grades.](https://example.com/table1)

<table>
<thead>
<tr>
<th>MRA grades</th>
<th>A (N = 59)</th>
<th>B (N = 25)</th>
<th>C (N = 15)</th>
<th>D (N = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 1</td>
<td>N = 7</td>
<td>N = 5</td>
<td>N = 2</td>
<td></td>
</tr>
</tbody>
</table>

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TABLE 1: Risk factors for the development of postoperative cerebral ischemic events

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Postop Ischemic Events (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of cases</td>
<td>16</td>
<td>90</td>
</tr>
<tr>
<td>age (yrs)*</td>
<td>67.7 ± 6.0</td>
<td>69.1 ± 6.2</td>
</tr>
<tr>
<td>male sex</td>
<td>16 (100.0)</td>
<td>87 (96.7)</td>
</tr>
<tr>
<td>hypertension</td>
<td>15 (93.8)</td>
<td>70 (77.8)</td>
</tr>
<tr>
<td>diabetes mellitus</td>
<td>8 (50.0)</td>
<td>34 (37.8)</td>
</tr>
<tr>
<td>hyperlipidemia</td>
<td>6 (37.5)</td>
<td>37 (41.1)</td>
</tr>
<tr>
<td>symptomatic lesions</td>
<td>13 (81.3)</td>
<td>65 (72.2)</td>
</tr>
<tr>
<td>bilat lesions</td>
<td>6 (28.6)</td>
<td>19 (22.4)</td>
</tr>
<tr>
<td>degree of ICA stenosis (%)*</td>
<td>91.9 ± 2.2</td>
<td>85.7 ± 7.8</td>
</tr>
<tr>
<td>duration of ICA clamping (mins)*</td>
<td>35.8 ± 6.4</td>
<td>36.2 ± 4.4</td>
</tr>
<tr>
<td>reduced MCA signal intensity</td>
<td>14 (87.5)</td>
<td>29 (34.1)</td>
</tr>
</tbody>
</table>

* Values presented as the means ± SD.

ate analyses) were adopted as confounders in the logistic regression model for the multivariate analysis: hypertension, degree of ICA stenosis, and reduced MCA signal intensity. The analysis revealed that only reduced MCA signal intensity was significantly associated with the development of postoperative cerebral ischemic events (95% CI 2.775–62.367, p = 0.0012).

When reduced MCA signal intensity was defined as impairment of cerebral hemodynamics, the sensitivity and specificity of the MR angiography grading in predicting the development of postoperative cerebral ischemic events were 88 and 63%, respectively. Using this same definition, positive- and negative-predictive values were 30% and 97%, respectively.

Figure 3 provides pre- and postoperative diffusion weighted MR images obtained in a patient with preoperative Grade C MR angiography signal (Fig. 1) who developed hemiparesis after CEA.

Discussion

The present study demonstrated that signal intensity of the MCA on preoperative single-slab 3D TOF MR angiography is useful in identifying patients at risk for cerebral ischemic events after CEA.

In a recent systematic review of the literature, the authors reported that 10% of patients undergoing CEA develop new postoperative ischemic lesions in the cerebral hemisphere ipsilateral to the site of CEA on diffusion weighted MR imaging performed within 72 hours after surgery.21 Taking into consideration the fact that our patients underwent diffusion weighted MR imaging earlier (within 24 hours after surgery), the incidence in the present study (13%) is consistent with previous findings. Hemodynamic cerebral ischemia due to hemispheric cerebral hypoperfusion during ICA clamping, as well as emboli from the surgical site, play significant roles in the development of new cerebral ischemic events immediately after CEA.15,24,25 While a “rosary-like pattern in the centrum semiovalis” of cerebral ischemic lesions on diffusion weighted MR imaging suggests a hemodynamic mechanism due to hemispheric cerebral hypoperfusion, “spotty” ischemic lesions suggest embolism.26 In the present study, all new postoperative ischemic lesions on diffusion weighted MR images were spotty and 3 of the 5 patients with new postoperative neurological deficits had such lesions. Thus, these 3 patients may have experienced symptomatic cerebral embolism. By contrast, the remaining 2 patients had new postoperative neurological deficits without new postoperative ischemic lesions noted on diffusion weighted MR imaging. However, because neither direct nor indirect measurement of hemispheric hypoperfusion during ICA clamping or of microemboli from the surgical site was performed in the present study, the precise mechanism for the new postoperative neurological deficits remains unknown.

Hemodynamic compromise due to chronic cerebral ischemia in ICA stenosis implies an inadequate collateral blood flow and insufficient vasodilatory capacity to maintain the cerebral blood flow against a further decrease in perfusion pressure. Because ICA clamping during CEA may cause a critical reduction of cerebral perfusion in areas with hemodynamic compromise, cerebral ischemic events may develop more frequently in patients with hemodynamic compromise than in those without. In fact, several investigators have demonstrated that a reduction of preoperative cerebrovascular reactivity to acetazolamide measured by brain perfusion SPECT correlates with a high risk for significant cerebral ischemia during ICA clamping.12

Microembolic signals on intraoperative transcranial Doppler ultrasonographic MCA examination are detected in > 90% of patients undergoing CEA.1,22,28 In particular, there is a significant correlation between the number of microembolic signals during dissection of the carotid arteries and development of new postoperative ischemic lesions on diffusion weighted MR imaging.1,22,28 According to the concept proposed by Caplan and Hennerici,4 low blood flow velocity in the cerebral artery may impair clearance of emboli generated from a proximal lesion, and this may facili-
tate the onset of ischemia due to emboli in poorly perfused areas of the brain. The blood flow velocity in the MCA is proportional to the cerebral mean transit time.\textsuperscript{16,20} Measurement of the mean transit time is also a sensitive method of estimating cerebrovascular reactivity to acetazolamide.\textsuperscript{21} Furthermore, increased mean transit time values correlate well with decreased cerebrovascular reactivity to acetazolamide as determined by brain perfusion SPECT.\textsuperscript{8,10} Thus, cerebrovascular reactivity to acetazolamide may conversely identify low MCA blood flow velocity. Indeed, a recent study has demonstrated that reduced preoperative cerebrovascular reactivity to acetazolamide measured by brain perfusion SPECT predicts the development of new postoperative cerebral ischemic lesions—on diffusion weighted MR imaging—that are caused by microemboli generated during carotid dissection in patients undergoing CEA.\textsuperscript{2} Because the present MR angiography method can detect reduction of cerebrovascular reactivity to acetazolamide measured by brain perfusion SPECT in the cerebral hemispheres with ICA stenoocclusive diseases,\textsuperscript{9} the present findings support the theory that preoperative hemodynamic impairment in the cerebral hemisphere ipsilateral to the surgical site is associated with development of cerebral ischemic events due to intraoperative emboli, as well as secondary to significant hemispheric hypoperfusion during ICA clamping.

In the present study, when the reduced MCA signal intensity on MR angiography was defined as impairment of cerebral hemodynamics, the MR angiography grade provided 88% sensitivity and 63% specificity, with a 30% positive- and 97% negative-predictive value for predicting development of postoperative cerebral ischemic events. Whereas the negative-predictive value was high, the positive-predictive value was considerably lower than that in patients in whom SPECT showed a reduced cerebrovascular reactivity to acetazolamide.\textsuperscript{2,9} We previously reported that the present MR angiography method provided 86% sensitivity, 70% specificity, a 51% positive-predictive value, and a 93% negative-predictive value for detecting hemispheres with SPECT-measured reduced cerebrovascular reactivity to acetazolamide.\textsuperscript{8} Thus, the low positive-predictive and the high negative-predictive values for detecting hemodynamic impairment in the present MR angiography method may account for the low positive-predictive and the high negative-predictive values for postoperative cerebral ischemic events, respectively.

This study possesses several limitations. First, the signal intensity of the MCA on MR angiography was visually graded using a subjective process. However, our previous study demonstrated that the inter- and intraobserver agreements of these measurements were excellent.\textsuperscript{4} Second, in contrast to the 3.0-T MR model used in the present study, most institutions commonly use a 1.5-T MR imager. While use of a 1.5-T MR imager for 3D TOF MR angiography results in inferior depiction of intracranial arteries because of lower spatial resolution and lower signal-to-noise ratio with decreased T1 relaxation time,\textsuperscript{22} MR angiography is more sensitive and specific for decreased velocity of inflowing blood with a 1.5-T than with a 3.0-T MR imager. Thus, the use of a 1.5-T system may be suitable for identifying patients at risk for cerebral ischemic events after CEA in conjunction with this method.

Although SPECT with an acetazolamide challenge is a reliable method for identifying patients with hemodynamic impairment,\textsuperscript{14,15} the clinical use of SPECT is precluded by its high cost and limited availability. In addition, acetazolamide is associated with frequent various adverse side effects, including metabolic acidosis, hypokalemia, numbness of the extremities, headache, tinnitus, gastrointestinal disturbances, and Stevens-Johnson syndrome.\textsuperscript{4,20} Recent studies have demonstrated that measurements of cerebral blood volume by perfusion weighted MR imaging with gadolinium can also identify patients with hemodynamic impairment.\textsuperscript{7} However, the contrast agents may be associated with the development of nephrogenic systemic fibrosis in the setting of renal insufficiency.\textsuperscript{23} By contrast, the present MR angiography method does not require administration of radioisotope or contrast agents, and its short scanning time is well suited for clinical screening tests.

**Conclusions**

The present study demonstrated that MCA signal intensity on preoperative single-slab 3D TOF MR angiography is useful in identifying patients at risk for cerebral ischemic events after CEA.

**Disclaimer**

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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