Diagnostic Impact of Transcranial Color-Coded Real-Time Sonography With Echo Contrast Agents for Hyperperfusion Syndrome After Carotid Endarterectomy

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Background and Purpose—The purpose of the present study was to evaluate availability of transcranial color-coded real-time sonography (TCCS) to detect hyperperfusion after carotid endarterectomy (CEA).

Methods—This prospective study included 105 consecutive patients who underwent CEA for severe carotid stenosis. TCCS with echo contrast agents was performed serially to evaluate flow velocity of the middle cerebral artery (MCA). Regional cerebral blood flow (rCBF) and vasodilatory capacity of the MCA territory were evaluated using single-photon emission computed tomography. We compared the changes in MCA flow velocity with rCBF.

Results—Using echo contrast agents, we could evaluate the MCA flow in 95 (90%) of 105 patients. Twelve patients showed hyperperfusion syndrome. Changes in the MCA mean flow velocity (MFV) before and 4 days after CEA were significantly correlated with those in rCBF ($r$=0.48; $P<0.0001$). An increase of >50% in MCA MFV was observed within 4 days after CEA in all 12 patients with hyperperfusion syndrome. Multivariate analysis revealed that reduced vasodilatory capacity (odds ratio, 0.14; 95% CI, 0.04 to 0.46) was an independent risk factor for a 1.5-fold increase in the MFV of MCA ipsilateral to CEA.

Conclusions—Findings of a 1.5-fold increase in the MCA MFV can accurately identify those patients with high risk of developing post-CEA hyperperfusion syndrome. TCCS with echo contrast agents is available for the evaluation of hyperperfusion after CEA. (Stroke. 2004;35:000-000.)

Key Words: carotid endarterectomy ■ cerebral blood flow ■ ultrasonography, Doppler, transcranial ■ contrast media

Hyperperfusion syndrome is well known as a significant complication after carotid endarterectomy (CEA). In previous studies, hyperperfusion syndrome was not shown to be frequent, but it was found to be fatal once an intracranial hemorrhage occurred.4,5 Thus, frequent evaluations of cerebral hemodynamics after CEA are required to watch for development of the syndrome. Because single-photon emission computed tomography (SPECT) and positron emission tomography for the measurement of regional cerebral blood flow (rCBF) are expensive, complicated, and time consuming, they may not be the appropriate modalities to use repeatedly after CEA.

Several studies have demonstrated the usefulness of transcranial Doppler (TCD) to monitor the flow velocity of the middle cerebral artery (MCA) after CEA and thus to predict the occurrence of hyperperfusion syndrome.3–6 However, the accuracy of TCD for measuring MCA flow velocity remained controversial. One can more readily and confidently identify particular vascular structure with transcranial color-coded real-time sonography (TCCS) than with TCD.7,8 A limiting factor in TCCS use as a screening tool is its relatively low sensitivity in detecting intracranial arteries (≈60% to 70%) because of an inadequate temporal bone window, especially in elderly patients.7,8 However, echo contrast agents have improved the quality of TCCS significantly.9,10

The purpose of this study was to evaluate the availability and accuracy of MCA flow velocity as measured by TCCS with echo contrast agents in detecting hemispheric hyperperfusion syndrome after CEA.

Subjects and Methods

Patients
A total of 105 consecutive patients who underwent CEA for carotid stenosis in our Cerebrovascular Center from September 2001 to September 2003 were included prospectively in the study. All patients gave informed consent to undergo cerebral angiography and CEA.
In accordance with American Heart Association guidelines, we adopted the following criteria as indications for CEA: (1) carotid stenosis of ≥70%, or 50% to 69% with repeated ischemic cerebrovascular events or severe ulcerative atheroma; (2) modified Rankin scale ≤2; (3) small or no brain infarction on MRI; and (4) absence of significant occlusive disease (≥70% in diameter) distal to the carotid stenosis. The degree of carotid stenosis was assessed using cerebral digital subtraction angiography with the method documented in the North American Symptomatic Carotid Endarterectomy Trial (NASCET) study. Six patients underwent bilateral CEA. The second CEA was performed 0.9 to 8.4 months (mean 4.3 months) after the first CEA.

Surgical Procedure

All CEA procedures were performed by the same neurosurgical team. Endarterectomy was performed using a microscope. After CEA, propofol sedation was continued until the next morning. Blood pressure was controlled using nitroglycerin and/or diltiazem until 7 days after CEA so that it was <150 mm Hg systolic and 90 mm Hg diastolic in all patients.

Clinical Diagnosis of Hyperperfusion Syndrome

After CEA, clinical and neurological symptoms were observed. Probable hyperperfusion syndrome was diagnosed if the patient deteriorated for focal seizure, temporary deterioration of consciousness level with remarkably abnormal speech and conduct for >6 hours after stopping propofol sedation, development of focal neurological signs such as motor weakness, or intracranial hemorrhage on computed tomography (CT). Temporary consciousness level deterioration within 6 hours after stopping anestesia and sedation was regarded as an anesthetic effect. If a patient was diagnosed as having a hyperperfusion syndrome, cranial CT and MRI studies were performed immediately. All patients underwent MRI 14 days after CEA. After CEA, blood pressure was also monitored in all patients. An increase in blood pressure was a reference criterion for the diagnosis of hyperperfusion syndrome. When a remarkable increase in blood pressure occurred within 7 days after CEA, CT studies were performed to evaluate whether ischemic or hemorrhagic changes were shown. Clinical diagnosis of hyperperfusion syndrome was done by a neurosurgeon who was blinded to TCCS findings.

TCCS Studies

A commercially available real-time 2D TCCS system (model HDI-5000; ATL Ultrasound) with a 2.5-MHz transducer for B-mode imaging and Doppler functions was used. The transducer was placed on the temporal surface. Particular care was taken to display a long-axis view of the horizontal portion of the MCA as a color flow on the B-mode image. Range-gated pulsed Doppler ultrasound with a sample volume length of 2 mm was used to measure MCA blood flow velocity. The incident angle between MCA and the Doppler beam was kept at ≤60°. Absolute values of peak systolic, end diastolic, and mean flow velocity (MPV) of ipsilateral or bilateral MCAs were measured using the maximum frequency envelope. TCCS studies were performed serially before, 1 hour, 1 day, 4 days, and 7 days after CEA. When ipsilateral MCA flow could not be displayed because of an inadequate temporal bone window, TCCS studies were repeated after intravenous echo contrast agent administration (300 mg/mL of Levovist; Schering).

Changes in MCA MFV were expressed using the following equation: MFV ratio = MFV after CEA/MFV before CEA.

Carotid Ultrasonography

Before CEA, conventional carotid duplex ultrasonography was performed to evaluate the carotid stenosis grade. The HDI-5000 with the 12-to-5-MHz linear array transducer was used. The maximum area and linear percent stenosis were measured. Transoral carotid ultrasonography (TOCU) was also performed to evaluate the portion distal to the carotid stenosis before and 2 weeks after CEA according to a method described previously. A 9-to-5-MHz convex array transducer was used. The diameter and flow velocity of the extracranial internal carotid artery (ICA) were measured at the nearest point from the surface of the posterior pharyngeal wall.

SPECT Studies

Cerebral hemodynamics were evaluated using SPECT before, 4 days after, and 14 days after CEA. The SPECT apparatus was the PRISM 2000X (2-head SPECT system; Picker), and 99mTc-ethyl cysteinate dimmer was used as the tracer. An elliptical region of interest (ROI) ≥16 cm2 in size was located in the cortical area in the MCA territory of each side. Areas of infarct, if present, were excluded from the ROI. rCBF values were measured quantitatively using the Patlack plot method before, 4 days after, and 14 days after CEA. rCBF values were also measured after the acetazolamide (ACZ) challenge test before and 14 days after CEA. Vasodilatory capacity (ACZ reactivity) was expressed using the following equation: ACZ reactivity = [(post-ACZ CBF − resting rCBF)/resting rCBF]×100. ACZ reactivity was classified into 3 groups: remarkably reduced ACZ reactivity (group A; ≤10%); slightly reduced ACZ reactivity (group B; >10% and <20%); and normal ACZ reactivity (group C; ≥20%).

Changes in rCBF of the MCA territory were expressed using the following equation: CBF ratio = rCBF after CEA/rCBF before CEA.

Data Analysis

The relationships between the occurrence of a hyperperfusion syndrome and changes in MCA flow velocities after CEA were investigated. Clinical and radiological factors that could predict the occurrence of hyperperfusion syndrome after CEA were also studied. For univariate analysis, the χ² test, paired t test, and 2-way repeated-measures ANOVA were used. Linear-regression analysis and the Pearson correlation coefficient were used to evaluate the correlation between changes in MCA territory CBF and MCA flow velocity. Logistic regression analysis was done for multivariate analysis. A P value of <0.05 was considered significant.

Results

Patient Demographics

Ninety men and 15 women aged 68.4 ± 7.4 (mean ± SD) years were included. Carotid lesions were symptomatic in 67 patients (64%) and asymptomatic in 38 (36%). The National Institutes of Health Stroke Scale (NIHSS) scores for symptomatic patients ranged between 1 and 10 (median 3). The carotid stenosis grade as determined by the NASCET method was 79.7 ± 14.3%.

MCA Flow Detection by TCCS

Because of an insufficient temporal bone window, ipsilateral MCA flows were invisible with conventional TCCS in 38 (36%) of 105 patients. In these 38 patients, 28 additional MCA flows could be observed by TCCS using echo contrast agents. Therefore, the sensitivity of the method for detecting an MCA flow was 90% (95 of 105). All 95 patients were included in the data analysis.

Clinical Observations

No complications were observed during CEA procedures. After propofol sedation was stopped the morning after CEA, focal seizures were present in 3 patients (3%), and temporary deterioration of consciousness level with remarkably abnormal speech and conduct occurred in 9 patients (9%). Among 6 patients with bilateral CEA, I had hyperperfusion syndrome after the second CEA. Of the 95 patients, 12 patients (13%) were suspected to have hyperperfusion syndrome. The syndrome occurred on the first postsurgical day for 8 patients, the second day for 2, the fourth day for 1, and the fifth day for 1.
No new hemorrhagic or ischemic lesions were detected in any patients during cranial CT or MRI within 4 days after CEA and MRI 14 days after CEA. Although 2 patients with focal seizure had hyperintense area in the ipsilateral parieto-occipital cortex on diffusion-weighted MRI just after the onset of the symptom, it disappeared after a 14-day follow-up MRI. Postsurgical blood pressure was somewhat high in patients with hyperperfusion syndrome compared with patients without hyperperfusion 1 hour after (127±17/64±8 versus 118±19/59±9 mm Hg), 1 day after (149±20/72±9 versus 136±25/63±13 mm Hg), 4 days after (151±15/79±11 versus 136±14/72±10 mm Hg), and 7 days after (147±21/71±14 versus 140±13/68±9 mm Hg) CEA.

Changes in MCA Flow Velocity and CBF in MCA Territory

MCA MFV increased significantly in the 12 patients with hyperperfusion syndromes 1 day after CEA (89.6±28.6 cm/s) compared with before the procedure (48.6±12.9 cm/s; P<0.0001). On the other hand, MCA MFV did not increase in the remaining 83 patients (from 60.0±13.0 cm/s to 62.8±20.3 cm/s). MCA MFV was lower in patients with hyperperfusion syndrome than without before CEA (48.6±12.9 versus 60.0±13.0 cm/s; P<0.001) and higher 1 day after CEA (89.6±28.6 versus 62.8±20.3 cm/s; P<0.05). In patients with hyperperfusion syndrome, the post-CEA MFV ratio was significantly higher than in patients without hyperperfusion (P<0.0001), with a peak in the ratio occurring 1 day after CEA (2.01±0.49; Figure 1).

Furthermore, in the 12 patients with post-CEA hyperperfusion syndrome, the CBF ratio 4 days after CEA was higher than in the 83 patients without hyperperfusion (1.24±0.11 versus 1.07±0.10; P<0.0001). There was no significant difference in CBF ratio 14 days after CEA between patients with and patients without hyperperfusion syndrome (1.06±0.15 versus 1.06±0.13). Of note, 4 days after CEA, MFV ratio was significantly correlated with CBF ratio (r=0.48; P<0.0001; Figure 2).

Relationships Between Hyperperfusion Syndrome and MFV Ratio

One day after CEA, 10 of 12 patients with hyperperfusion syndrome showed an MFV ratio of ≥1.5 (Figure 3). In these 10 patients, hyperperfusion syndrome occurred between 1 and 4 days after CEA. The remaining 2 patients had an MFV ratio between 1.4 and 1.5 1 day after CEA and >1.5 4 days after CEA. Both patients developed hyperperfusion syndrome between 4 and 7 days after CEA. Thus, a maximum MFV ratio of 1.5 within 4 postsurgical days was an appropriate cut-off value for the prediction of hyperperfusion syndrome. This cut-off yielded a sensitivity of 100% and a high specificity (84%). In the following analyses, we used this cut-off value as a hyperperfusion syndrome predictor.

Clinical, Radiological, and Ultrasonographical Findings and Increase in MFV in MCA

We examined the relationship of a maximum MFV ratio of ≥1.5 documented within 4 days after CEA as the optimal criterion for predicting postsurgical hyperperfusion syndrome and the clinical, radiological, and ultrasonographical data obtained before CEA. The following factors contributed to a prediction of the ratio >1.5: symptomatic carotid stenosis (P<0.01); NIHSS score (P<0.01); severe carotid stenosis using NASCET method (P<0.01); retrograde flow of the ophthalmic artery ipsilateral to the CEA detected by cerebral angiography.
TABLE 1. Clinical Factors to Predict Significant Increase in MCA Flow Velocity

<table>
<thead>
<tr>
<th>Maximum MFV Ratio</th>
<th>≥1.5 (n=25)</th>
<th>&lt;1.5 (n=70)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>67.8±7.8</td>
<td>68.6±7.2</td>
<td>NS</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>4 (16%)</td>
<td>6 (9%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>NIHSS score</td>
<td>1.84±2.85</td>
<td>0.67±1.77</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hypertension</td>
<td>22 (88%)</td>
<td>59 (84%)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10 (40%)</td>
<td>23 (33%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>11 (44%)</td>
<td>24 (34%)</td>
<td>NS</td>
</tr>
<tr>
<td>Carotid stenosis, %</td>
<td>9 (40%)</td>
<td>20 (29%)</td>
<td>NS</td>
</tr>
<tr>
<td>NASCET (angiogram)</td>
<td>87.1±14.5</td>
<td>77.3±13.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Area (ultrasonography)</td>
<td>92.9±6.0</td>
<td>89.4±8.1</td>
<td>NS</td>
</tr>
<tr>
<td>Linear (ultrasonography)</td>
<td>79.1±12.4</td>
<td>75.7±9.6</td>
<td>NS</td>
</tr>
</tbody>
</table>

(MFV of the ipsilateral distal ICA by TOCU (P<0.01) and MCA by TCCS (P<0.001); small diameter of the ipsilateral distal ICA by TOCU (P<0.01); and rCBF (P<0.05) and ACZ reactivity (P<0.001) in the ipsilateral MCA territories (Tables 1 and 2). Furthermore, depending on the grade of ACZ reactivity, there was a significant difference in the maximum MFV ratio (P<0.001; Figure 4).

Multivariate analysis was done on the above factors that had a statistically significant relationship with a maximum MFV ratio of ≥1.5 within 4 days after CEA. It was shown that the actual grade (A through C) of the reduced ACZ reactivity was an independent predictor for hyperperfusion syndrome (odds ratio, 0.14; 95% CI, 0.04 to 0.46).

Discussion

This is the first report that has evaluated TCCS accuracy for detecting hyperperfusion syndrome and determined the correlation between quantitatively measured flow velocity and CBF. This study resulted in 3 major findings. First, MFV of the MCA ipsilateral to CEA obtained using TCCS was able to detect hemispheric hyperperfusion syndrome after CEA. Second, a ≥1.5-fold increase in the MFV within 4 postsurgical days was a predictor of hyperperfusion syndrome and had complete sensitivity with high specificity. Third, as important evidence for prediction of hyperperfusion using MFV, the postsurgical MFV ratio significantly correlated with postsurgical CBF and presurgical ACZ reactivity in the affected MCA territory as assessed by SPECT.

There have been many studies in which hyperperfusion syndrome was monitored using TCD. However, because of questions regarding accuracy of TCD in diagnosing hyperperfusion syndrome, some controversy remained. Because precise placement of the sample volume as well as angle correlation is not possible by means of the TCD technique, TCD cannot determine absolute MCA flow velocity values. Tilting, rotating, or shifting of the actual location of the transducer during TCD can cause remarkable changes in flow velocity as a result of changes in the angle between the Doppler beam and the horizontal portion of the MCA. Inaccurate observation of the MCA using TCD might cause a high frequency of false-positive hyperperfusion syndrome diagnoses. For example, in the study by Dalman et al4 with 123 subjects, TCD sensitivity for diagnosing hyperperfusion syndrome was 100%, but specificity was only 53%. In contrast, when using TCCS, one can evaluate the change in absolute value of MCA flow velocity. As well, the MFV ratio was significantly correlated with the CBF ratio.

When hyperperfusion syndrome is suspected, a strict treatment regime should be implemented immediately. Before proceeding with treatment, ability to predict hyperperfusion syndrome accurately would be desirable. In previous studies using TCD, the diagnostic criterion of hyperperfusion syndrome was mostly a ≥2-fold increase in MCA peak systolic or MFV after CEA. In this study, an MFV ratio of ≥1.5
within 4 postsurgical days yielded a sensitivity of 100% and a specificity of 84%. An MFV ratio of ≥1.4 the next morning after CEA was another indicator that predicted hyperperfusion syndrome perfectly, although its specificity was relatively low (67%). A maximum MFV ratio cut-off value of 2 within 4 postsurgical days yielded a sensitivity of 75% and a specificity of 99%. In our hospital, when an MFV ratio of ≥1.5 was observed within 4 days after CEA, the patients received more strict blood pressure control with or without a continuation of propofol sedation until the next TCCS evaluation. Propofol decreases the cerebral oxygen metabolism with a consequent CBF reduction. As well, with cerebral dysautoregulation, a decrease in systemic blood pressure could result directly in a CBF decrease. This might be the reason that CBF increase in present patients after CEA was not so high compared with previous studies in which the CBF increase in the ipsilateral MCA territory was ≥100%.1,18,19

For multivariate analysis, reduction of presurgical ACZ reactivity in the affected MCA territory was an independent predictor for an MFV ratio of >1.5 within 4 postsurgical days. Several studies have also shown an association between impaired vasodilatory capacity and hyperperfusion syndrome. Moreover, intraoperative transcranial regional cerebral oxygen saturation is another essential indicator for post-CEA hyperperfusion syndrome.1 Ascher et al demonstrated that contralateral CEA within 3 months was associated with post-CEA hyperperfusion syndrome;1 1 of 6 patients with bilateral CEA had the syndrome in this study.

A study limitation is high frequency of post-CEA hyperperfusion syndrome (13%) compared with that in previous studies (1% to 3%).2,22,23 Difference in diagnostic criteria for the syndrome might be a reason for the frequency variance between studies. Especially, consciousness deterioration and headache are frequent symptoms for post-CEA patients, which often but not always indicate hemispheric hyperperfusion. To select patients strictly with hyperperfusion syndrome, we regarded deterioration of consciousness level with remarkably abnormal speech and conduct for >6 hours after stopping sedation as presenting hyperperfusion syndrome. We did not regard patients presenting only headache as having the syndrome.

In conclusion, MFV ratio can be measured serially using TCCS with echo contrast agents, and it reflects changes in cerebral hemodynamics after CEA. Using the MFV ratio, we can accurately predict which patients are in the high-risk group for developing hyperperfusion syndrome.

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References
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