Postoperative Cortical Neural Loss Associated With Cerebral Hyperperfusion and Cognitive Impairment After Carotid Endarterectomy

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Background and Purpose—Although cerebral hyperperfusion after carotid endarterectomy (CEA) often impairs cognitive function, MRI does not always demonstrate structural brain damage associated with postoperative cognitive impairment. The purpose of the present study was to determine whether postoperative cortical neural loss, which can be detected by $^{123}$I-iomazenil single-photon emission CT, is associated with cerebral hyperperfusion after CEA and whether it correlates with postoperative cognitive impairment.

Methods—In 60 patients undergoing CEA for ipsilateral internal carotid artery stenosis (>70%), cerebral blood flow was measured using N-isopropyl-$^{123}$I-iodoamphetamine single-photon emission CT before and immediately after CEA and on the third postoperative day. The distribution of benzodiazepine receptor binding potential in the cerebral cortex was assessed using $^{123}$I-iomazenil single-photon emission CT before and 1 month after surgery and was analyzed using 3-dimensional stereotactic surface projection. Neuropsychological testing was also performed preoperatively and at the first postoperative month.

Results—Post-CEA hyperperfusion and postoperative cognitive impairment were observed in 9 patients (15%) and 8 patients (13%), respectively. Post-CEA hyperperfusion was significantly associated with postoperative hemispheric reduction of benzodiazepine receptor binding potential (95% CIs, 2.765 to 148.804; $P=0.0031$). Post-CEA hyperperfusion (95% CIs, 1.183 to 229.447; $P=0.0370$) and postoperative hemispheric reduction of benzodiazepine receptor binding potential (95% CIs, 1.003 to 77.381; $P=0.0496$) were also significantly associated with postoperative cognitive impairment.

Conclusions—Cerebral hyperperfusion after CEA results in postoperative cortical neural loss that correlates with postoperative cognitive impairment. (Stroke. 2009;40:448-453.)

Key Words: carotid endarterectomy ▪ cerebral hyperperfusion ▪ cognitive impairment ▪ neural loss

Cerebral hyperperfusion after carotid endarterectomy (CEA) is defined as a major increase in ipsilateral cerebral blood flow (CBF) after surgical repair of carotid stenosis that is well above the metabolic demands of the brain tissue. Cerebral hyperperfusion syndrome after CEA is characterized by unilateral headache, face and eye pain, seizures, and focal symptoms related to cerebral edema or intracerebral hemorrhage. Although the prognosis of patients with intracerebral hemorrhage is poor, the incidence of intracerebral hemorrhage is relatively low (approximately 1%). Furthermore, neurological deficits in patients who developed cerebral hyperperfusion syndrome without experiencing subsequent intracranial hemorrhage tend to be reversible, because there is no major destruction of the neural tissue due to intracranial hemorrhage. By contrast, recent studies have demonstrated that asymptomatic cerebral hyperperfusion after CEA is often detected on CBF imaging and that it results in impairments in cognitive function. Indeed, cerebral hyperperfusion syndrome, even when it is not complicated with intracerebral hemorrhage, results in persistent impairment of cognitive function, which adversely affects patients’ quality of life. However, MRI, including diffusion- and T2-weighted imaging, does not always demonstrate structural brain damage associated with postoperative cognitive impairment.

The distribution of central benzodiazepine receptors in the human brain has been widely studied with single-photon emission CT (SPECT) using $^{123}$I-iomazenil (IMZ). Benzodiazepine receptor binding potential on $^{123}$I-IMZ SPECT images correlates with brain neural density, and a reduction in...
cortical benzodiazepine receptor binding indicates cortical neural damage or loss.\textsuperscript{10–12} The purpose of the present study was to determine whether postoperative cortical neural loss, which can be detected by \textsuperscript{123}I-IMZ SPECT, is associated with cerebral hyperperfusion after CEA and whether it correlates with postoperative cognitive impairment.

**Methods**

**Subjects**

Sixty patients with ipsilateral internal carotid artery (ICA) stenosis (≥70\%) and useful residual function (modified Rankin disability scale 0, 1, or 2) who underwent CEA were enrolled in the present study. Fifty-six of the 60 patients were men and 4 were women. Mean age of the patient population was 68.6±6.8 years (mean±SD), ranging from 44 to 78 years. Concomitant disease states and symptoms were recorded, including 52 patients with hypertension, 21 patients with diabetes mellitus, and 31 patients with hyperlipidemia. Thirty-seven patients evinced ipsilateral carotid territory symptoms, including 11 patients with transient ischemic attacks, 6 patients with transient ischemic attacks and subsequent stroke, and 20 patients with stroke alone. Twenty-three patients had asymptomatic ICA stenosis. Preoperative MRI, including diffusion-weighted images, was performed immediately after surgery also underwent MRI on the day on which symptoms developed.

**Neuropsychological Evaluation**

A battery of neuropsychological tests was administered, consisting of the Japanese translation of the Wechsler Adult Intelligence Scale.
Revised (WAIS-R), the Japanese translation of the Wechsler Memory Scale, and Rey-Osterreith Complex Figure test (Rey test). WAIS-R provides measures of general intellectual function and generates a verbal and performance intelligence quotient (IQ). Wechsler Memory Scale assesses orientation, recall of current information, recall of passages, sustained attention, digit span, and new learning of associative word pairs. The Rey test evaluates constructional ability and visual memory. The subtests within the Rey test include the copy trial, in which the subject copies a drawing of a complex figure, and a recall trial, in which the subject draws the figure from memory after a 30- to 45-minute delay. Thus, 5 scores (WAIS-R verbal IQ, WAIS-R performance IQ, Wechsler Memory Scale, Rey copy, and Rey recall) were used to evaluate cognitive function.

The neuropsychological tests were performed before and 1 month after surgery. All examinations were administered by a trained neuropsychologist who was blinded to the patients' clinical information.

As controls, 44 patients with asymptomatic unruptured cerebral aneurysms (17 men and 27 women; 32 to 70 years of age; mean age, 56.8 years) underwent the same neuropsychological tests before and 1 month after neck clipping through craniotomy. None of the 44 patients had new postoperative neurological deficits and brain injury caused by surgery for the aneurysms on postoperative CT. Differences in each neuropsychological test score before and after neck clipping (postoperative scores–preoperative scores) were 2.4±4.6 (mean±SD) in the WAIS-R verbal IQ, 4.8±5.2 in the WAIS-R performance IQ, 2.9±8.1 in the Wechsler Memory Scale, 0.2±1.1 in the Rey copy, and 2.6±4.2 in the Rey recall. Thus, the mean −2 SD of the differences was −6.8 for the WAIS-R verbal IQ, −5.6 for the WAIS-R performance IQ, −13.3 for the Wechsler Memory Scale, −2.0 for the Rey copy, and −5.8 for the Rey recall. For the neuropsychological test scores of each patient undergoing CEA, a deficit was defined as a postoperative test score more than the absolute value of the mean −2 SDs of the difference less than the preoperative score. A patient was considered as having postoperative cognitive impairment when the patient had one or more postoperative neuropsychological scores with a deficit.

**Statistical Analysis**

Data are expressed as the mean±SD. The relationship between the area with postoperatively reduced BRBP and post-CEA hyperperfusion or postoperative cognitive impairment was evaluated using the Mann-Whitney U test. The relationship between each variable and postoperative hemispheric reduction of BRBP or postoperative cognitive impairment was evaluated by univariate analysis using the Mann-Whitney U test or χ² test. A multivariate statistical analysis of factors related to postoperative hemispheric reduction of BRBP or postoperative cognitive impairment 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.

**Results**

All patients recovered within 1 hour after surgery without new major neurological deficits. DWI performed 1 day after surgery showed new hyperintense lesions in the cerebral hemisphere ipsilateral to CEA in 14 (23%) of the 60 patients studied when compared with preoperative DWI. The diameter of all new hyperintense lesions was ≤1.5 cm.

Post-CEA hyperperfusion on SPECT imaging was observed in 9 patients (15%). In 7 of these 9 patients, hyperperfusion resolved in the SPECT performed on the third postoperative day, and pharmacological control of blood pressure was discontinued. These patients did not experience new neurological symptoms eventually. The remaining 2 patients with post-CEA hyperperfusion experienced a progressive increase in CBF on the third postoperative day and developed hyperperfusion syndrome. One of these patients experienced motor weakness of the upper and lower extremities in the side contralateral to surgery on the seventh postoperative day. Another patient experienced focal seizures as evidenced by motor disturbances of the upper extremity in the side contralateral to surgery 6 days after surgery. Coma was induced in these 2 patients. After termination of the propofol coma, these patients eventually experienced full recovery. None of the 9 patients with post-CEA hyperperfusion exhibited new lesions on MRI performed on the third postoperative day, the day on which symptoms developed, or at the first postoperative month.

The area with postoperatively reduced BRBP ranged from 1.7% to 14.5% (5.5%±2.8%) among the 60 patients studied. The area was significantly larger in patients with postoperative hyperperfusion than in those without (P<0.0001) and was significantly larger in patients with postoperative cognitive impairment than in those without (P<0.0001). Closed and open circles indicate patients with and without postoperative cognitive impairment, respectively. Arrows indicate patients with cerebral hyperperfusion syndrome.
higher in patients with postoperative hemispheric reduction of BRBP than in those without. Other variables were not significantly associated with postoperative hemispheric reduction of BRBP. After eliminating variables that were closely related to others, the following items with \( P < 0.2 \) in the univariate analyses were adopted as confounders in the logistic regression model for the multivariate analysis: hypertension, symptomatic lesion, infarction on preoperative MRI, degree of ICA stenosis, and postoperative hyperperfusion. The analysis revealed that only postoperative hyperperfusion was significantly associated with postoperative hemispheric reduction of BRBP (95% CIs, 2.765 to 148.804; \( P = 0.0031 \)).

At the postoperative neuropsychological assessment, 8 patients (13%) showed postoperative cognitive impairment. The area with postoperatively reduced BRBP was significantly larger in patients with postoperative cognitive impairment (9.7% ± 3.0%) than in those without (4.9% ± 2.1%; \( P = 0.0001 \); Figure 1). Results of univariate analysis of factors related to postoperative cognitive impairment are summarized in Table 2. The incidences of post-CEA hyperperfusion and postoperative hemispheric reduction of BRBP were significantly higher in patients with postoperative cognitive impairment.

### Table 1. Univariate Analysis of Factors Related to Postoperative Hemispheric Reduction of BRBP

<table>
<thead>
<tr>
<th>Variables</th>
<th>Postoperative Hemispheric Reduction of BRBP</th>
<th>Yes (n=11)</th>
<th>No (n=49)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean ± SD</td>
<td></td>
<td>69.3 ± 5.8</td>
<td>68.4 ± 7.1</td>
<td>0.7084</td>
</tr>
<tr>
<td>Male gender</td>
<td></td>
<td>11 (100%)</td>
<td>45 (92%)</td>
<td>&gt;0.9999</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td>8 (73%)</td>
<td>44 (90%)</td>
<td>0.1538</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td>4 (36%)</td>
<td>17 (35%)</td>
<td>&gt;0.9999</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td></td>
<td>4 (36%)</td>
<td>27 (55%)</td>
<td>0.3271</td>
</tr>
<tr>
<td>Symptomatic lesion</td>
<td></td>
<td>9 (82%)</td>
<td>28 (57%)</td>
<td>0.1778</td>
</tr>
<tr>
<td>Infarction on preoperative MRI</td>
<td></td>
<td>9 (82%)</td>
<td>26 (53%)</td>
<td>0.1010</td>
</tr>
<tr>
<td>Degree of ICA stenosis, %, mean ± SD</td>
<td></td>
<td>90.5±5.7</td>
<td>84.8±9.0</td>
<td>0.0455</td>
</tr>
<tr>
<td>Bilateral lesions</td>
<td></td>
<td>9 (82%)</td>
<td>39 (80%)</td>
<td>&gt;0.9999</td>
</tr>
<tr>
<td>Duration of ICA clamping, minutes, mean ± SD</td>
<td></td>
<td>37±6</td>
<td>36±5</td>
<td>0.4847</td>
</tr>
<tr>
<td>New ischemic lesions on DWI on the first postoperative day</td>
<td></td>
<td>3 (27%)</td>
<td>11 (22%)</td>
<td>0.7075</td>
</tr>
<tr>
<td>Postoperative hyperperfusion</td>
<td></td>
<td>6 (55%)</td>
<td>3 (6%)</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

### Table 2. Univariate Analysis of Factors Related to Postoperative Cognitive Impairment

<table>
<thead>
<tr>
<th>Variables</th>
<th>Yes (n=8)</th>
<th>No (n=52)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean ± SD</td>
<td>70.4±5.2</td>
<td>68.3±7.0</td>
<td>0.4318</td>
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<tr>
<td>Male gender</td>
<td>7 (88%)</td>
<td>71 (94%)</td>
<td>&gt;0.9999</td>
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<tr>
<td>Hypertension</td>
<td>5 (63%)</td>
<td>47 (90%)</td>
<td>0.0648</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3 (38%)</td>
<td>18 (35%)</td>
<td>&gt;0.9999</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>4 (50%)</td>
<td>27 (52%)</td>
<td>&gt;0.9999</td>
</tr>
<tr>
<td>Symptomatic lesion</td>
<td>6 (75%)</td>
<td>31 (60%)</td>
<td>0.6983</td>
</tr>
<tr>
<td>Infarction on preoperative MRI</td>
<td>6 (75%)</td>
<td>29 (56%)</td>
<td>0.4493</td>
</tr>
<tr>
<td>Degree of ICA stenosis, %, mean ± SD</td>
<td>88.8±7.4</td>
<td>85.4±8.9</td>
<td>0.2412</td>
</tr>
<tr>
<td>Bilateral lesions</td>
<td>7 (88%)</td>
<td>41 (79%)</td>
<td>&gt;0.9999</td>
</tr>
<tr>
<td>Duration of ICA clamping, minutes, mean ± SD</td>
<td>37±6</td>
<td>36±5</td>
<td>0.7937</td>
</tr>
<tr>
<td>New ischemic lesions on DWI on the first postoperative day</td>
<td>2 (25%)</td>
<td>12 (23%)</td>
<td>&gt;0.9999</td>
</tr>
<tr>
<td>Postoperative hyperperfusion</td>
<td>5 (63%)</td>
<td>4 (8%)</td>
<td>0.0011</td>
</tr>
<tr>
<td>Postoperative hemispheric reduction of BRBP</td>
<td>6 (75%)</td>
<td>5 (10%)</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

Figure 2. A 77-year-old man with symptomatic left ICA stenosis (95%) exhibiting cerebral hyperperfusion syndrome and cognitive impairment after carotid endarterectomy. A, \( N \)-isopropyl-\( p \)-\([123I]\)-iodoamphetamine SPECT shows hyperperfusion in the ipsilateral cerebral hemisphere immediately after surgery. B, Three-dimensional stereotactic surface projection images in A demonstrate pixels with postoperative hyperperfusion (red dots) occupying 56% of the entire ipsilateral cerebral cortex. C, \([123I]\)-iomazenil SPECT reveals a postoperative reduction of tracer uptake in the ipsilateral cerebral cortex. D, Three-dimensional stereotactic surface projection images in C demonstrate areas with postoperatively reduced BRBP (red dots) occupying 14.3% of the entire ipsilateral cerebral cortex. Eighty-three percent of the areas exhibit postoperative hyperperfusion when compared with B.
improvement than in those without. Other variables were not significantly associated with postoperative cognitive impairment. After eliminating variables that were closely related to others, the following items with $P<0.2$ in the univariate analyses were adopted as confounders in the logistic regression model for the multivariate analysis: hypertension, post-CEA hyperperfusion, and postoperative hemispheric reduction of BRBP. The analysis revealed that post-CEA hyperperfusion (95% CIs, 1.183 to 229.447; $P=0.0370$) and postoperative hemispheric reduction of BRBP (95% CIs, 1.003 to 77.381; $P=0.0496$) were significantly associated with postoperative cognitive impairment.

Figure 2 shows SPECT images in one patient with cerebral hyperperfusion syndrome and cognitive impairment after surgery.

**Discussion**

Previous studies have demonstrated that patients with asymptomatic cerebral hyperperfusion on CBF imaging do not exhibit new postoperative lesions on MRI and that even the reversible vasogenic or cytotoxic edema on MRI develops in less than half of patients with cerebral hyperperfusion syndrome. This is consistent with results from the present study. 123I-IMZ SPECT images in the present study displayed 123I-IMZ uptake in the cerebral cortex at 180 minutes after intravenous injection of the tracer. Investigators have demonstrated that these images are proportional to the distribution of benzodiazepine receptor binding potential. In addition, post-CEA hyperperfusion often develops in the ipsilateral cerebral cortex but not in the contralateral cerebral cortex. Thus, a significant postoperative reduction of 123I-IMZ uptake in the ipsilateral cerebral cortex relative to that in the contralateral cerebral cortex was defined as postoperatively reduced BRBP in the ipsilateral cerebral cortex. As a result, the area with postoperatively reduced BRBP was significantly larger in patients with post-CEA hyperperfusion than in those without, and postoperative hemispheric reduction of BRBP was significantly associated with postoperative cognitive impairment. These data suggest that cerebral hyperperfusion after CEA results in postoperative cortical neural loss and support the hypothesis that 123I-IMZ SPECT can detect neuronal damage that CT or MRI cannot.

Postoperative cortical neural loss may also occur through other mechanisms. For example, a significant number of patients have evidence of gaseous and particulate emboli in the middle cerebral artery during CEA. In addition, new ischemic lesions on DWI performed within a few days after surgery are seen in approximately 10% of patients undergoing CEA, and the number of embolic signals on transcranial Doppler ultrasonography high-intensity transient signal analysis generated during CEA is strongly correlated with postoperative evidence of new hyperintense lesions on DWI. In the present study, although DWI performed 1 day after surgery showed new ischemic lesions in the cerebral hemisphere ipsilateral to CEA in 23% of patients, the presence or absence of the lesions was not associated with postoperative hemispheric reduction of benzodiazepine receptor binding potential. Postoperative cortical neural loss may occur secondary to hemispheric hyperperfusion during CEA. Clamping of the carotid arteries during CEA results in a transient decrease in CBF in the ipsilateral middle cerebral artery territory in many patients. If the change in hemispheric CBF is significant enough to damage the cortical neurons, it may result in postoperative hemispheric reduction of benzodiazepine receptor binding potential. In the present study, the duration of ICA clamping was not associated with postoperative hemispheric reduction of benzodiazepine receptor binding potential, but the intensity of hyperperfusion during ICA clamping was not examined.

Cognitive impairment occurs in 10% to 30% of patients after CEA, and postoperative cerebral hyperperfusion is associated with impairment of cognitive function. However, MRI does not always demonstrate structural brain damage associated with postoperative cognitive impairment, which is consistent with results from the present study. By contrast, the area with postoperatively reduced BRBP was significantly larger in patients with postoperative cognitive impairment than in those without, and postoperative hemispheric reduction of BRBP was significantly associated with postoperative cognitive impairment. These findings suggest that cortical neural loss after CEA correlates with postoperative cognitive impairment and is consistent with previous findings that the degree of the decrease in benzodiazepine receptor binding is associated with the presence or absence of neurological symptoms.

A recent study investigated the significance of postoperative crossed cerebellar diaschisis in patients with post-CEA hyperperfusion. In that study, although crossed cerebellar diaschisis developed on the third postoperative day in patients that resulted in postoperative cognitive impairment associated with cerebral hyperperfusion, patients who developed post-CEA hyperperfusion without exhibiting subsequent crossed cerebellar diaschisis did not experience postoperative cognitive impairment. These findings suggest that post-CEA hyperperfusion-mediated reductions in cerebral metabolism result in cerebral dysfunction and cognitive impairment, which is also consistent with observations from the present study.

The present study possesses several limitations that require discussion. First, IMZ SPECT images were analyzed on a pixel-by-pixel basis using 3-dimensional stereotactic surface projection, and ΔAI with a value less than the mean − 2 SDs in the healthy volunteers was defined as postoperatively reduced BRBP. According to this definition, the threshold was less than −10.0 in 17% of a total of pixels. Thus, postoperatively reduced BRBP may be underestimated in this study.

Second, although neuropsychological tests are regarded as good measures of postoperative cognitive impairment, the criterion for defining a significant impairment in neuropsychological test can vary. Heyer et al assessed patients undergoing CEA and lumbar spine surgery with a battery of pre- and postoperative neuropsychological tests and defined patients undergoing spine surgery as a control group. Fur-
thermore, they defined significant cognitive dysfunction as performance that exceeded 2 SDs above the mean performance of patients in the control group. The present study defined patients with asymptomatic unruptured cerebral aneurysms who uneventfully underwent neck clipping through craniotomy as a control group. Although all 5 neuropsychological tests scores were postoperatively increased on average due to the “practice effect” (an improvement in scores when patients are repeatedly tested), the definition of postoperative neuropsychologic deficits in the present study may have underestimated the true prevalence of deficits when compared with other studies.

Conclusions
The present study demonstrated that cerebral hyperperfusion after CEA results in postoperative cortical neural loss that correlates with postoperative cognitive impairment.

Disclosures
None.

References
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