Preoperative Cerebral Hemodynamic Impairment and Reactive Oxygen Species Produced During Carotid Endarterectomy Correlate With Development of Postoperative Cerebral Hyperperfusion

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Background and Purpose—The purpose of the present study was to determine whether preoperative cerebral hemodynamic impairment and reactive oxygen species produced during carotid endarterectomy (CEA) correlate with development of postoperative cerebral hyperperfusion.

Methods—Concentrations of malondialdehyde-modified low-density lipoprotein (MDA-LDL), a biochemical marker of oxidative damage, were measured in serum samples obtained from 90 patients undergoing CEA for ipsilateral ICA stenosis (>70%). Serum samples were obtained from a venous catheter inserted into the ipsilateral jugular bulb before clamping of the internal carotid artery (ICA), 10 minutes after clamping of the ICA, and 5 and 20 minutes after declamping of the ICA. Cerebral blood flow (CBF) and cerebrovascular reactivity (CVR) to acetazolamide were also measured using single-photon emission computed-tomography before CEA. In addition, CBF was measured postoperatively.

Results—Hyperperfusion (CBF increase >100% compared with preoperative values) was observed immediately after CEA in 12 patients (13%). Logistic regression analysis demonstrated that reduced preoperative CVR (95% CIs, 1.053 to 1.453; \( P = 0.0097 \)) and an increase in MDA-LDL (calculated as a percentage of the preclamp values) after ICA declamping (95% CIs, 0.862 to 0.980; \( P = 0.0098 \)) were significantly associated with development of postoperative cerebral hyperperfusion among the variables tested. Ten of 11 patients with reduced preoperative CVR and increased MDA-LDL after ICA declamping developed post-CEA hyperperfusion, and 2 of these patients developed cerebral hyperperfusion syndrome.

Conclusions—Both preoperative cerebral hemodynamic impairment and reactive oxygen species produced during surgery correlate with development of cerebral hyperperfusion after CEA. (Stroke. 2007;38:2712-2717.)

Key Words: carotid endarterectomy ■ cerebral hemodynamic impairment ■ cerebral hyperperfusion ■ reactive oxygen species

Most complications after carotid endarterectomy (CEA) are ischemic in nature, either secondary to embolization or to inadequate cerebral protection in patients with poor collateral supply.\(^1\) Postoperative neurological dysfunction may also be related to cerebral hyperperfusion, which is defined as a major increase in ipsilateral cerebral blood flow (CBF) well above the metabolic demands of the brain tissue.\(^2\) 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.\(^2\) Although the incidence of intracerebral hemorrhage is relatively low (0.4 to 1.8%), the prognosis for patients with intracerebral hemorrhage is poor.\(^2\) Further, a recent study has demonstrated that postoperative cerebral hyperperfusion, even when asymptomatic, results in impaired cognitive function in patients undergoing CEA.\(^2\)

Risk factors for cerebral hyperperfusion include long-standing hypertension, high-grade stenosis, poor collateral blood flow, and contralateral carotid occlusion, which often impairs cerebral hemodynamic reserve.\(^3\) A rapid restoration of normal perfusion pressure after CEA may result in hyperperfusion in a region of the brain with impaired autoregulation attributable to chronic ischemia. This hypothesis is similar to the “normal perfusion pressure breakthrough” theory described by Spetzler et al.\(^4\) In fact, several investigators have demonstrated that decreased cerebrovascular reactivity (CVR) to acetazolamide is a significant predictor of post-CEA hyperperfusion.\(^1,5,16\) However, whereas post-CEA hyperperfusion is not observed in patients with normal...
preoperative CVR, patients with impaired cerebral hemodynamic reserve do not always develop post-CEA hyperperfusion.1,15,16 Thus, additional factors may be associated with the development of post-CEA hyperperfusion.

Reactive oxygen species are produced in the central nervous system during reperfusion after ischemia and cause postischemic hyperperfusion or brain edema.17–20 Because CEA represents a discrete episode of focal cerebral ischemia followed by reperfusion, several investigators have suggested that there may be significant production of reactive oxygen species in the brain after declamping of the internal carotid artery (ICA) during CEA.17,21–25 Further, one study has demonstrated that pretreatment with the novel free radical scavenger, edaravone, prevents occurrence of cerebral hyperperfusion after CEA,26 which suggests contribution of reactive oxygen species to the pathogenesis of post-CEA hyperperfusion.

Oxidized low-density lipoprotein is a biochemical marker of oxidative damage,27–29 and plasma concentration of oxidized low-density lipoprotein reportedly correlates with infarct size in patients with acute cerebral infarction.29 Recently, a method for accurate measurement of serum malondialdehyde-modified low-density lipoprotein (MDA-LDL), one of the oxidized low-density lipoproteins, has been established.25,30 Thus, the purpose of the present study was to determine whether preoperative cerebral hemodynamic impairment and reactive oxygen species produced during CEA correlate with postoperative cerebral hyperperfusion.

Subjects and Methods

Subjects

Ninety patients with ipsilateral ICA stenosis (>70%) and useful residual function (modified Rankin disability scale 0, 1, or 2) who underwent CEA were enrolled in the present study. Eighty-six of the 90 patients were men, and 4 were women. Mean age of the patient population was 67.9±7.5 years (mean ± SD), ranging from 44 to 78 years. Concomitant disease states and symptoms were recorded, including 78 patients with hypertension, 31 patients with diabetes mellitus, and 42 patients with hyperlipidemia. Fifty-five patients evinced ipsilateral carotid territory symptoms, including 16 patients with transient ischemic attacks (TIAs), 10 patients with TIAs and subsequent stroke, and 29 patients with stroke alone. Thirty-five patients had asymptomatic ICA stenosis. Preoperative magnetic resonance (MR) imaging demonstrated infarction in the hemisphere ipsilateral to the ICA stenosis in 32 patients and no infarction in 58 patients. All patients underwent preoperative angiography with arterial catheterization. Overall average degree of ICA stenosis was 84.9±8.7%, with a range of 70% to 95%, according to the method of the North American Symptomatic Carotid Endarterectomy Trial.31 The contralateral ICA was occluded in 6 patients, and 17 additional patients had 70% to 95% stenosis.

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

Single Photon Emission Computed Tomography

CBF was assessed using N-isopropyl-p-[123I]-iodoamphetamine (IMP) and single photon emission computed tomography (SPECT) before and immediately after CEA. CVR to acetazolamide was also measured for evaluation of cerebral hemodynamic reserve before CEA. In addition, patients with cerebral hyperperfusion immediately after CEA underwent a third CBF measurement in the same manner, 3 days after CEA. Preoperative SPECT study was performed more than 1 month after the last ischemic event and 7 to 10 days before CEA.

SPECT studies were performed using a ring-type SPECT scanner (Headtome-SET080, Shimadzu Corp), which provided 31 tomographic images simultaneously. The spatial resolution of the scanner with a low-energy, all-purpose collimator was 13 mm FWHM at the center of the field of view, and the slice thickness was 25 mm FWHM at the field of view center. Image slices were taken at 5-mm center-to-center spacing, parallel to the orbitomeatal line. The images were reconstructed using the weighted-filtered backprojection technique, in which the attenuation correction was made by detecting the edge of the object. An attenuation coefficient of 0.065 cm⁻¹, a Butterworth filter (cutoff = 0.45 cycle/cm; order = 3), and a ramp filter were used for image reconstruction.

The IMP SPECT study with acetazolamide challenge was performed as described previously.32 After a 1-minute intravenous infusion of 22 MMBq of [123I]IMP (5-mL volume) at a constant rate of 5 mL/min and a 1-minute infusion of physiological saline at the same rate, data acquisition was performed at a midscan time of 30 minutes after the IMP administration for a scan duration of 20 minutes. Two days after the measurement of the CBF at the resting state, subjects underwent SPECT with acetazolamide challenge. Acetazolamide (1000 mg, range 13 to 19 mg/kg body weight) was dissolved in physiological saline (20 mL), and the solution was administered intravenously over a period of one minute. Ten minutes later, IMP was administered, and the SPECT study was performed using the same procedure as that used during the resting state. The CBF images were calculated according to the IMP-autoradiography method.32,33 In each image slice obtained immediately after CEA, a large irregular region of interest (ROI) of 16 cm² or more was manually and bilaterally drawn in the entire cerebral cortex. These ROIs were placed in regions where infarction was not present, as confirmed by preoperative magnetic resonance (MR) imaging. After the CBF was determined in each ROI, the ratio of ipsilateral regional CBF (I) to contralateral regional CBF (C) (I/C ratio) was calculated, according to the IMP-autoradiography method.32,33 The control values of CBF at resting state and CVR were 9.4±4.4 mL/100 g/min and 36.8±9.2%, respectively. When the values of CVR were less than the mean−2SD, (ie, 18.4%), they were considered reduced CBF. Post-CEA hyperperfusion was defined as CBF increase of >100% (ie, a doubling) compared with preoperative values, according to Piepras et al.3
blood pressure was discontinued. However, when hyperperfusion persisted, systolic arterial blood pressure was maintained below 140 mm Hg. When hyperperfusion syndrome developed, the patient was placed in propofol coma. A diagnosis of hyperperfusion syndrome required: (1) seizure, deterioration of consciousness level and/or development of focal neurologic signs such as motor weakness, and (2) hyperperfusion on the SPECT performed after CEA without findings of any additional ischemic lesion on postoperative CT scan or MR imaging.

**Intraoperative Sample Collection and MDA-LDL Assay**

For all patients, 10 mL of blood was obtained intraoperatively from the venous catheter inserted into the ipsilateral jugular bulb at the following time points: immediately before clamping of the ICA; 10 minutes after clamping of the ICA; 5 minutes after declamping of the ICA; and 20 minutes after declamping of the ICA. All blood samples were immediately centrifuged at 3000 rpm for 10 minutes, and the serum layer was aspirated and stored at −70°C until analysis. Serum MDA-LDL concentration was measured using a standard enzyme-linked immunosorbent assay, as described elsewhere. The MDA-LDL data for each patient were normalized such that the values immediately before clamping of the ICA were assigned a value of 100% and the values at 10 minutes after clamping of the ICA, at 5 and 20 minutes after declamping of the ICA were calculated as a percentage of the preclamp values (%MDA-LDL). Because the peak of %MDA-LDL after declamping of the ICA was unknown, higher values of %MDA-LDL at either 5 or 20 minutes after ICA declamping in each patient were defined as post-declamp %MDA-LDL.

**Statistical Analysis**

Data are expressed as the mean±SD. Differences between concentrations of %MDA-LDL at each time point were examined by repeated measured ANOVA followed by Scheffé multiple comparisons. The relationship between each variable and the development of cerebral hyperperfusion after CEA was evaluated with univariate analysis using the Mann–Whitney U test or χ² test. A multivariate statistical analysis of factors related to development of cerebral hyperperfusion after CEA 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, and no patients exhibited additional ischemic lesions on CT and MR imaging that was performed on the first and third postoperative day, respectively.

![Figure 1. Changes in %MDA-LDL in the jugular bulb during carotid endarterectomy. Error bars indicate ±1SD.](image)

Table 1. Univariate Analysis of Factors Related to the Development of Cerebral Hyperperfusion After CEA

<table>
<thead>
<tr>
<th>Variables</th>
<th>Yes (n=12)</th>
<th>No (n=78)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (mean±SD)</td>
<td>71.1±3.3</td>
<td>67.4±7.8</td>
<td>0.1419</td>
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<tr>
<td>Male sex</td>
<td>11 (92%)</td>
<td>75 (96%)</td>
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<td>Hypertension</td>
<td>12 (100%)</td>
<td>60 (77%)</td>
<td>0.1146</td>
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<td>Diabetes mellitus</td>
<td>6 (50%)</td>
<td>25 (32%)</td>
<td>0.3274</td>
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<tr>
<td>Hyperlipidemia</td>
<td>7 (58%)</td>
<td>35 (45%)</td>
<td>0.5363</td>
</tr>
<tr>
<td>Symptomatic lesion</td>
<td>10 (83%)</td>
<td>45 (58%)</td>
<td>0.1176</td>
</tr>
<tr>
<td>Infarction on preoperative MR imaging</td>
<td>5 (42%)</td>
<td>27 (34%)</td>
<td>0.7483</td>
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<tr>
<td>Degree of ICA stenosis, % (mean±SD)</td>
<td>89.0±6.8</td>
<td>84.3±8.9</td>
<td>0.0557</td>
</tr>
<tr>
<td>Bilateral lesions</td>
<td>4 (33%)</td>
<td>19 (24%)</td>
<td>0.4945</td>
</tr>
<tr>
<td>Preoperative CVR, % (mean±SD)</td>
<td>9.6±8.6</td>
<td>32.2±17.2</td>
<td>&lt;0.0001</td>
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<tr>
<td>Duration of ICA clamping, min (mean±SD)</td>
<td>37.0±3.7</td>
<td>35.9±4.4</td>
<td>0.3913</td>
</tr>
<tr>
<td>Post-declamp %MDA-LDL, % (mean±SD)</td>
<td>150.1±21.3</td>
<td>119.1±21.9</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

CEA indicates carotid endarterectomy; SD, standard deviation; MR, magnetic resonance; ICA, internal carotid artery; CVR, cerebrovascular reactivity; MDA-LDL, malondialdehyde-modified low-density lipoprotein.

All 90 patients underwent SPECT study within 2 hours after declamping of the ICA. Twelve patients (13%) met the CBF criteria for post-CEA hyperperfusion on the SPECT imaging. CBF values, as measured before, immediately after, and 3 days after surgery in 12 patients with post-CEA hyperperfusion, were 28.0±2.9, 60.6±6.1 and 43.7±11.1 mL/100g/min, respectively. CBF before and immediately after surgery in 78 patients without post-CEA hyperperfusion were 32.0±5.0 and 35.9±6.1 mL/100g/min, respectively. Whereas post-CEA hyperperfusion was observed in 12 (52%) of 23 patients with reduced preoperative CVR, none of patients with normal preoperative CVR (n=67) developed post-CEA hyperperfusion.

Results of univariate analysis of factors related to the development of cerebral hyperperfusion after CEA are summarized in Table 1. Preoperative CVR and post-declamp %MDA-LDL in patients with postoperative cerebral hyperperfusion were significantly lower and higher than those in patients without postoperative cerebral hyperperfusion, respectively. Other variables were not significantly associated with the development of postoperative cerebral hyperperfusion. 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: age, hypertension, symptomatic lesion, degree of ICA stenosis, preoperative CVR, and post-declamp %MDA-LDL. The odds ratios for these variables after multivariate analysis are shown in Table 2. The analysis revealed that preoperative CVR and post-declamp %MDA-LDL were significantly associated with the development of postoperative cerebral hyperperfusion.

When the values of the post-declamp %MDA-LDL more than 140% were rated as elevated post-declamp %MDA-LDL, 10 (91%) of 11 patients with reduced preoperative CVR and elevated post-declamp %MDA-LDL developed post-CEA hyperperfusion (Figure 2). One of these 2 patients experienced confusion and left motor weakness 4 days after surgery (Figure 3). The other patient experienced a focal seizure as evidenced by motor disturbances of the left upper extremity on the sixth postoperative day. Propofol coma was induced in both patients. Eventually, both patients experienced full recovery after termination of propofol coma. Patients without hyperperfusion immediately after CEA (n=78) did not develop hyperperfusion syndrome for the remainder of the study.

**Discussion**

In the present study, concentrations of serum MDA-LDL in the jugular bulb after ICA declamping were significantly increased compared with those before clamping of the ICA. Several investigators have showed significant elevations in malondialdehyde, diene conjugates, or lipoperoxides, all of

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cerebral Hyperperfusion</th>
<th>OR</th>
<th>95% CIs</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (mean ± SD)</td>
<td>71.1 ± 3.3</td>
<td>67.4 ± 7.8</td>
<td>0.880</td>
<td>0.593–1.306</td>
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<tr>
<td>Hypertension</td>
<td>12 (100%)</td>
<td>60 (77%)</td>
<td>1.456</td>
<td>0.408–5.200</td>
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<tr>
<td>Symptomatic lesion</td>
<td>10 (83%)</td>
<td>45 (58%)</td>
<td>0.502</td>
<td>0.041–6.102</td>
</tr>
<tr>
<td>Degree of ICA stenosis, % (mean ± SD)</td>
<td>89.0 ± 6.8</td>
<td>84.3 ± 8.9</td>
<td>1.043</td>
<td>0.874–1.243</td>
</tr>
<tr>
<td>Preoperative CVR, % (mean ± SD)</td>
<td>9.6 ± 8.6</td>
<td>32.2 ± 17.2</td>
<td>1.237</td>
<td>1.053–1.453</td>
</tr>
<tr>
<td>Post-declamp %MDA-LDL (mean ± SD)</td>
<td>150.1 ± 21.3</td>
<td>119.1 ± 21.9</td>
<td>0.919</td>
<td>0.862–0.980</td>
</tr>
</tbody>
</table>

In 10 of 12 patients with post-CEA hyperperfusion, hyperperfusion resolved in the SPECT performed on the third postoperative day, and pharmacologic control of blood pressure was discontinued. These patients did not experience new neurological symptoms eventually. However, in the remaining 2 patients who exhibited reduced preoperative CVR and elevated post-declamp %MDA-LDL, hyperperfusion persisted and hyperperfusion syndrome developed (Figure 2).

**Figure 2.** Preoperative cerebrovascular reactivity (CVR) and post-declamp %MDA-LDL. Ten of 12 patients with postoperative cerebral hyperperfusion are located in the quadrant with preoperative CVR less than the mean ± 2SD of the normal control value (dashed vertical line) and post-declamp %MDA-LDL more than 140% (dashed horizontal line). Closed and open circles indicate patients with and without cerebral hyperperfusion immediately after surgery, respectively. Arrows indicate patients with cerebral hyperperfusion syndrome.

**Figure 3.** A 66-year-old man with asymptomatic right internal carotid artery stenosis (95%) exhibiting hyperperfusion syndrome after carotid endarterectomy. Preoperative single-photon emission computed-tomography (SPECT) shows poor acetazolamide-induced increases in right hemispheric perfusion (left). Post-declamp %MDA-LDL in the patient was 175% and hyperperfusion in the ipsilateral hemisphere is observed on SPECT immediately after carotid endarterectomy (right). This patient developed confusion and left motor weakness 4 days after surgery.
which are indices of free radical-induced lipid peroxidation, in jugular vein plasma immediately after declamping of the ICA in patients undergoing CEA. Others have reported a significant decrease in jugular venous plasma antioxidant potential when comparing values before ICA clamping to those after ICA declamping as well as a decrease in antioxidant capacity across the cerebral circulation. Another study using electron spin resonance spin trapping techniques directly demonstrated the production of free radicals during ICA clamping and after ICA declamping. Data from the present study are consistent with these previous reports and suggest that there was significant production of reactive oxygen species in the brain after declamping of the ICA.

Previous studies have reported that patients with reduced preoperative CVR to acetazolamide have a high risk of developing post-CEA hyperperfusion, which is consistent with results from the present study. This supports the theory that hyperperfusion results from loss of normal vasoconstriction secondary to chronic cerebral ischemia and maladaptive autoregulatory mechanisms. However, patients with reduced preoperative CVR do not always develop post-CEA hyperperfusion. In fact, in the present study, the incidence of post-CEA hyperperfusion in patients with reduced preoperative CVR was 52%.

The present study demonstrated that the MDA-LDL increase after ICA declamping is also significantly associated with development of postoperative cerebral hyperperfusion. Indeed, 91% of patients with reduced preoperative CVR and elevated post-declamp %MDA-LDL developed post-CEA hyperperfusion. These data demonstrated that in addition to preoperative cerebral hemodynamic impairment, reactive oxygen species produced during CEA correlate with postoperative cerebral hyperperfusion. Although the basic mechanisms of cerebrovascular autoregulation remain controversial, the cerebrovascular endothelial cells may play a major role in this process, possibly via production of relaxing (eg, nitric oxide) or contractile factors. The reactive oxygen species produced during ischemia-reperfusion damage the endothelial cells, resulting in impairment of cerebrovascular autoregulation. Thus, reactive oxygen species produced by clamping and declamping of the ICA during CEA may deteriorate further cerebrovascular autoregulation that is already impaired by preoperative chronic ischemia. This process likely culminates in post-CEA hyperperfusion.

In the present study, no patients with a combination of normal preoperative CVR and elevated post-declamp %MDA-LDL developed post-CEA hyperperfusion. All these patients recovered from surgery without new major neurological deficits, and postoperative CT scan and MR imaging did not detect additional ischemic lesions. Thus, reactive oxygen species alone produced by clamping and declamping of the ICA may not be sufficient to provoke post-CEA hyperperfusion in patients with cerebral ischemia that is as severe as the brain is not damaged.

The present study possesses one notable limitation that requires discussion; namely, an intraluminal shunt was not used intraoperatively in any of the patients studied. A recent study has suggested that the degree of production of reactive oxygen species after ICA declamping during CEA correlates with the intensity of the cerebral ischemia, which peaks several minutes after ICA clamping but does not correlate with the duration of ICA clamping. Further, Weigand et al reported that even reperfusion after short-term cerebral ischemia (ICA clamping for 6 minutes) significantly enhanced cerebral lipid peroxidation. In fact, the incidence of hyperperfusion in patients undergoing CEA with the use of an intraluminal shunt has been reported to be 8% to 11%, which is consistent with data from the present study.

Conclusion

The present study demonstrated that both preoperative cerebral hemodynamic impairment attributable to chronic ischemia and reactive oxygen species produced during surgery correlate with development of cerebral hyperperfusion after CEA.

Disclosures

None.

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