Postoperative cerebral hyperperfusion associated with impaired cognitive function in patients undergoing carotid endarterectomy

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Object. Cognitive impairment occurs in 20 to 30% of patients following carotid endarterectomy (CEA). The purpose of the present study was to determine whether postoperative cerebral hyperperfusion is associated with impairment of cognitive function in patients undergoing that procedure.

Methods. Cerebral blood flow (CBF) was measured using single-photon emission computerized tomography scanning before and immediately after CEA and on the 3rd postoperative day in 92 patients with ipsilateral internal carotid artery stenosis of 70% or greater. Hyperperfusion post-CEA was defined as a 100% increase or greater in CBF compared with preoperative values. Neuropsychological testing was also performed preoperatively and at the 1-, 3-, and 6-month follow-up examinations.

At the 1-month postoperative neuropsychological assessment, 11 patients (12%) displayed evidence of cognitive impairment. In addition, the incidence of postoperative cognitive impairment in patients with post-CEA hyperperfusion (seven [58%] of 12 patients) was significantly higher than that in patients without post-CEA hyperperfusion (four [5%] of 80 patients; p < 0.0001). A logistic regression analysis demonstrated that post-CEA hyperperfusion was the only significant independent predictor of postoperative cognitive impairment. Of the seven patients in whom post-CEA hyperperfusion and cognitive impairment were identified 1 month postoperatively, four (including three patients with hyperperfusion syndrome) remained cognitively impaired at the 3- and 6-month follow-up examinations.

Conclusions. Postoperative cerebral hyperperfusion is associated with impairment of cognitive function in patients undergoing CEA. Furthermore, the development of hyperperfusion syndrome is associated with the persistence of postoperative cognitive impairment.

Key Words: carotid endarterectomy • cognition • hyperperfusion

Cerebral hyperperfusion after CEA is defined as a major increase in ipsilateral CBF that is far greater than the metabolic demands of brain tissue following the surgical repair of CA stenosis. A rapid restoration of normal perfusion pressure following CEA may result in hyperperfusion in a region of the brain with impaired autoregulation due to chronic ischemia. This hypothesis is similar to the “normal perfusion pressure breakthrough” theory described by Spetzler, et al.

Cerebral hyperperfusion syndrome following CEA is a complication of cerebral hyperperfusion that is characterized by a unilateral headache, face and eye pain, seizure, and focal symptoms caused by cerebral edema or ICH. Although the incidence of ICH is relatively low (0.4–1.8%), the prognosis for this condition is poor. Several investigators have advocated strict control of blood pressure during the postoperative period to prevent ICH due to hyperperfusion. Carotid endarterectomy is an effective means of preventing stroke in appropriately selected patients. Although the incidence of major morbidity caused by perioperative stroke is low, cognitive decline, as revealed by neuropsychological testing, occurs in 20 to 30% of patients following CEA. Whereas intraoperative hemispheric cerebral ischemia or microemboli may play a significant role in the development of postoperative cognitive impairment, the relationship between cerebral hyperperfusion following CEA with postoperative cognitive impairment has not been investigated.

The purpose of this study was to determine whether postoperative cerebral hyperperfusion was associated with impairment in cognitive function in patients undergoing CEA.

Clinical Material and Methods

Patient Population

Between May 1997 and January 2002, 106 patients with ipsilateral ICA stenosis of 70% or greater and useful revascularization were identified for the study. Exclusion criteria included the following: age < 18 years; stroke within 1 month of the planned procedure; severe cerebral ischemia (National Institute of Health Stroke Scale > 12) or severe cerebral infarction (NIHSS > 12); prior stroke within 3 months of the procedure; urgent surgery; and previous cerebrovascular procedures. All patients underwent duplex scanning of the extracranial carotid arteries and blood pressure measurement preoperatively. The study was approved by the institutional ethics committee, and informed consent was obtained from all patients.

Cerebral blood flow was measured using single-photon emission computerized tomography (SPECT) before and immediately after CEA and on the 3rd postoperative day in 92 patients with ipsilateral internal carotid artery stenosis of 70% or greater. Hyperperfusion post-CEA was defined as a 100% increase or greater in CBF compared with preoperative values. Neuropsychological testing was also performed preoperatively and at the 1-, 3-, and 6-month follow-up examinations.

At the 1-month postoperative neuropsychological assessment, 11 patients (12%) displayed evidence of cognitive impairment. In addition, the incidence of postoperative cognitive impairment in patients with post-CEA hyperperfusion (seven [58%] of 12 patients) was significantly higher than that in patients without post-CEA hyperperfusion (four [5%] of 80 patients; p < 0.0001). A logistic regression analysis demonstrated that post-CEA hyperperfusion was the only significant independent predictor of postoperative cognitive impairment. Of the seven patients in whom post-CEA hyperperfusion and cognitive impairment were identified 1 month postoperatively, four (including three patients with hyperperfusion syndrome) remained cognitively impaired at the 3- and 6-month follow-up examinations.

Conclusions. Postoperative cerebral hyperperfusion is associated with impairment of cognitive function in patients undergoing CEA. Furthermore, the development of hyperperfusion syndrome is associated with the persistence of postoperative cognitive impairment.

Key Words: carotid endarterectomy • cognition • hyperperfusion

Abbreviations used in this paper: CA = carotid artery; CBF = cerebral blood flow; CEA = carotid endarterectomy; CT = computerized tomography; ICA = internal carotid artery; ICH = intracerebral hemorrhage; IMP = [123I]N-isopropyl-p-iodoamphetamine; MCA = middle cerebral artery; MR = magnetic resonance; PIQ = performance intelligence quotient; ROCF = Rey–Osterreith Complex Figure; ROI = region of interest; SD = standard deviation; SPECT = single-photon emission CT; TIA = transient ischemic attack; VIQ = verbal intelligence quotient; WAIS-R = Wechsler Adult Intelligence Scale, Revised; WMS = Wechsler Memory Scale.

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sidual function (modified Rankin Scale Score 0, 1, or 2) underwent CEA consecutively. Of these 106 patients, 92 entered the present study, whereas five patients who had undergone CEA in combination with coronary bypass surgery and nine patients who had been unable to perform the neuropsychological evaluation in Japanese were excluded.

Eighty-one patients were men and 11 were women. The mean age of the patient population was 67.7 ± 5.5 years (mean ± SD) and ranged from 50 to 75 years. Concomitant disease states and symptoms were recorded: there were 70 patients with hypertension, 31 patients with diabetes mellitus, 32 patients with coronary artery disease, and 18 patients with lower-extremity atherosclerotic occlusive disease. Fifty patients evinced symptoms of the ipsilateral CA territory; 15 experienced TIAs alone, eight patients experienced TIAs and a subsequent stroke, and 27 patients suffered a stroke alone. Forty-two patients exhibited asymptomatic CBF images were obtained according to the IMP autoradiography method. While in a state of general anesthesia, all patients underwent CEA more than 1 month after the last ischemic event. Intraluminal shunt-and-patch grafts were not used in these procedures. The mean duration of ICA clamping was 32 minutes (range 17–45 minutes).

Patients with and without cerebral hyperperfusion immediately after CEA underwent MR imaging and CT scanning, respectively, on the 1st postoperative day to confirm the presence or absence of additional ischemic lesions.

In patients with post-CEA hyperperfusion, arterial blood pressure was closely monitored and strictly maintained between 100 and 140 mm Hg by intravenous administration of nicardipine given while the patients were in the intensive care unit. When CBF decreased and hyperperfusion resolved on the 3rd postoperative day, pharmacological control of a patient’s blood pressure was discontinued. If hyperperfusion persisted, however, systolic arterial blood pressure was maintained below 90 mm Hg. A diagnosis of hyperperfusion syndrome required the following: 1) seizure, deterioration in the patient’s consciousness level, and/or development of focal neurological signs such as motor weakness; and 2) evidence of hyperperfusion on the IMP-SPECT scan obtained after CEA without any finding of an additional ischemic lesion on a postoperative CT or MR image. When hyperperfusion syndrome did occur, a barbiturate coma was induced.

In patients without post-CEA hyperperfusion, administration of aspirin was initiated on the day after surgery. In contrast, aspirin was not administered to patients with post-CEA hyperperfusion until CBF imaging indicated that the hyperperfusion had resolved.

Neuropsychological Evaluation

A battery of neuropsychological tests given to patients included the Japanese version of the WAIS-R, the Japanese translation of the WMS, and the ROCF test. The WAIS-R provides measures of general intellectual function and generates a VIQ and PIQ. The WMS assesses orientation, recall of current information, recall of passages, sustained attention, digit span, and new learning of associative word pairs. The ROCF test is used to evaluate copy and recall of a complex figure, thereby assessing the patient’s visuospatial constructive ability and visual memory. Subtests within the ROCF test include the copy trial, in which the patient copies a drawing of a complex figure, and a recall trial, in which the patient draws the figure from memory after a 30- to 45-minute delay. Thus, five scores (the WAIS-R VIQ, WAIS-R PIQ, WMS, ROCF copy, and ROCF recall) were used to evaluate cognitive function. High scores in these neuropsychological tests imply high levels of cognitive function.

The neuropsychological tests were performed 1 month before and 1 month after surgery. In addition, patients in whom cognitive impairment was identified at the 1-month follow-up examination underwent a third and fourth set of neuropsychological tests at 3 and 6 months after surgery, respectively. All examinations were administered by a trained neuropsychologist (K.Y.), who was blinded to the patients’ clinical information.

Statistical Analysis

Data are expressed as the means ± SDs. The patients’
neuropsychological performances were evaluated in two ways: by a group-rate analysis and by an event-rate analysis. In the former, a paired t-test on the five neuropsychological scores was used. In the latter, we applied a conventional definition of postoperative neuropsychological deficit that has been widely used in studying the impact of cardiac surgery. An SD unit for each test was computed from all the preoperative scores. A deficit occurred in a test when the patient’s postoperative score dropped one or more SD units from the preoperative score. Patients were considered to have postoperative cognitive impairments when one or more of the postoperative neuropsychological scores demonstrated a deficit. The incidence of postoperative cognitive impairment in patients with and those without post-CEA hyperperfusion was compared by performing a chi-square test. A logistic regression analysis was performed to determine the joint effect of multiple variables on cognitive impairment after CEA. Covariates included the patient’s age, sex, side of operation, complications (hypertension and diabetes mellitus), presence of a symptomatic lesion, infarction on MR images, bilateral lesions, degree of ICA stenosis, duration of ICA cross-clamping, and post-CEA hyperperfusion. Differences were deemed statistically significant if the probability value was less than 0.05.

Results

Regardless of the presence or absence of cerebral hyperperfusion immediately after CEA, all patients recovered within 1 hour after surgery without any new major neurological deficit, and no additional ischemic lesions were observed on MR images or CT scans obtained on the 1st postoperative day.

Hyperperfusion post-CEA was observed on SPECT images in 12 patients (13%). In nine of these patients, SPECT scans obtained on the 3rd postoperative day demonstrated that the hyperperfusion had resolved; thus pharmacological control of blood pressure was discontinued. The remaining three patients with post-CEA hyperperfusion experienced a progressive increase in CBF on the 3rd postoperative day and hyperperfusion syndrome developed. One of these patients experienced a focal seizure, as evidenced by motor disturbances of the right upper extremity 6 days after surgery. Two other patients experienced confusion and motor weakness on the 5th and 6th postoperative day, respectively. Barbiturate coma was induced in these three patients. Following termination of the barbiturate coma, these patients eventually experienced full recovery.

The incidence of postoperative cognitive impairment in patients with post-CEA hyperperfusion (seven [58%] of 12 patients) was significantly higher than that in patients without post-CEA hyperperfusion (four [5%] of 80 patients; \( p < 0.0001 \)). The logistic regression analysis demonstrated that post-CEA hyperperfusion was the only significant independent predictor of postoperative cognitive impairment (Table 2). Even when we excluded the four patients in whom new neurological symptoms developed during the postoperative period (for example, the three patients with hyperperfusion syndrome and the one patient with asymptomatic hyperperfusion and symptomatic cerebral ischemia), the results of logistic regression analysis demonstrated that post-CEA hyperperfusion was the only significant independent predictor of postoperative cognitive impairment (\( p = 0.031 \)).

In the 11 patients with postoperative cognitive impairment, the number of neuropsychological test scores that demonstrated a deficit at 1, 3, and 6 months postoperative-
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Table 3: Neuropsychological test scores demonstrating a deficit in patients with postoperative cognitive impairments

<table>
<thead>
<tr>
<th>Timing of Test</th>
<th>No. of Patients w/ Post-CEA Hyperperfusion (7 patients)</th>
<th>No. of Patients w/o Post-CEA Hyperperfusion (4 patients)</th>
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<tbody>
<tr>
<td>1 mo postop</td>
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<td>1</td>
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<td>5</td>
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<tr>
<td>3 mos postop</td>
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<td></td>
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<td>6 mos postop</td>
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Discussion

The present study demonstrates that postoperative cerebrovascular hyperperfusion is associated with impairment of cognitive function in patients undergoing CEA.

In numerous studies, changes in cognitive functioning have been investigated following CEA.1,2,18,20,27,41 Although an improvement in cognition after CEA was reported in slightly more than half of these studies, no change was found in the remainder. It is noteworthy that these studies are likely affected by differences in various methodological factors, including sample size, types of patient and control groups, severity and side of the CA stenosis, and range of neuropsychological testing. Timing of the postoperative assessment may also affect the results.16,20,41 Neuropsychological tests performed at the 1-month follow-up examination, as in the present study, may not allow a sufficient time after surgery and general anesthesia to yield satisfactory data on the patient’s true cognitive impairment. Thus, we also performed neuropsychological testing 3 and 6 months postoperatively in patients in whom cognitive impairment had been demonstrated at 1 month postoperatively. It is important to note that there are no clear guidelines for determining a significant improvement in performance, because such an improvement may in part reflect the practice effect (an improvement in score when a patient is repeatedly tested).15,27 In the present study, although four of five neuropsychological tests scores demonstrated a significant postoperative improvement in the group-rate analysis, the change in each mean score was minimal. We can infer from these findings that there is no significant clinical improvement in cognitive function following CEA. In contrast, the event-rate analysis showed that cognitive impairment occurred in 12% of patients following CEA, a lower incidence than that reported previously.6,16 Whereas neuropsychological tests are regarded to be good measures of postoperative cognitive impairment,15 the criteria for defining a significant impairment in a neuropsychological test can vary.26 Heyer, et al.16 examined patients undergoing CEA and lumbar spine surgery by performing a battery of pre- and postoperative neuropsychological tests and compared these patients with a control group of patients undergoing spine surgery. Furthermore, they defined a significant cognitive dysfunction as performance that exceeded two SDs greater than the mean performance of patients in the control group. As a result, cognitive dysfunction was seen 1 month postoperatively in 23% of patients who had undergone CEA. For the postoperative neuropsychological deficit, we considered a decrease of at least one SD unit from the preoperative score to be significant. This does not obviate the problem encountered when using a fixed numerical decrease as a definition for cognitive impairment; in that system, it is difficult to designate postoperative cognitive impairment in those patients who score significantly below the mean on the preoperative examination.13 Therefore, in comparison with deficits in previous studies, postoperative neuropsychological deficits may be underestimated in the present study.

Most investigators have hypothesized that cognitive impairment after CEA may result from the following two mechanisms.3,6,7,12,15,16 First, to perform a CEA, the ICA and common CA are cross-clamped. There is a transient decrease in CBF in the ipsilateral MCA territory in many patients.13,51 If the change in the hemispheric CBF is significant enough to change neuron function, there may be a change in electroencephalographic signals, which may result in intraoperative stroke. Indeed, patients in whom changes in electroencephalographic signals are identified have a higher probability of having a stroke.4,19 An intraoperative ischemic stroke can cause postoperative impairment of cognitive function. Another mechanism is intraoperative microemboli. A large percentage of patients have evidence of gaseous and particulate emboli in the MCA during CEA.12,47 Although several investigators have demonstrated that particulate embolization during the dissection period correlated with neuropsychological deterioration,12,26
other investigators have shown no significant correlation between intraoperative emboli and neuropsychological score changes. Thus, the cause of postoperative cognitive impairment has not been definitively established. Fearn and colleagues have recently reported that deterioration in attention was related to a rise in MCA flow velocity after the ICA had been unclamped. Although the authors did not refer to the underlying mechanism for this effect in their discussion, their findings indicate a correlation between cerebral hyperperfusion following CEA and postoperative cognitive impairment. Data in the present study have demonstrated that postoperative cerebral hyperperfusion, even when asymptomatic, was associated with impairment of cognitive function in patients undergoing CEA.

There are several explanations to account for the association of cerebral hyperperfusion and cognitive impairment. First, T2-weighted or diffusion-weighted MR imaging has demonstrated hyperintense lesions in the region corresponding to hyperperfusion observed on CBF imaging, and these lesions indicate cytotoxic edema. Although patients with post-CEA hyperperfusion and cognitive impairment did not always exhibit obviously hyperintense lesions on MR imaging, obvious or occult cytotoxic edema may cause postoperative cognitive impairment. Second, significant and global cerebral ischemia due to clamping of the ICA or cerebral embolism during CEA can lead to reperfusion hyperemia. In the present study, however, all patients with post-CEA hyperperfusion recovered within 1 hour after surgery without new neurological deficits, and MR imaging performed on the 1st postoperative day demonstrated no additional ischemic lesions. These findings indicate that the patients did not have severe intraoperative cerebral ischemia, and it is unlikely that intraoperative cerebral ischemia alone can account for post-CEA hyperperfusion. Alternatively, preoperative hemodynamic impairment (reduction of acetazolamide-induced changes in CBF) caused by chronic ischemia has been reported as a significant independent predictor of post-CEA hyperperfusion. Thus, whereas the hemispheric cerebral ischemia alone can account for post-CEA hyperperfusion, even when asymptomatic, cognitive impairment in patients undergoing CEA.

Of the 12 patients with post-CEA hyperperfusion according to CBF studies, one patient who had asymptomatic stenosis of the contralateral ICA as a result of undergoing CEA also experienced a TIA due to hyperperfusion during pharmacological control of blood pressure. Cognitive function in this patient was impaired at the 1-, 3-, and 6-month follow-up examinations. These findings compel us to propose that pharmacological control of blood pressure may induce hyperperfusion in the cerebral hemisphere contralateral to the CEA, leading to ischemic brain damage and cognitive impairment. Although strict control of blood pressure during the postoperative period is effective in preventing cerebral hyperperfusion syndrome, additional study is required to determine whether the treatment can reduce the incidence of postoperative cognitive impairment in patients with stenotic–occlusive lesions of the contralateral ICA following CEA.

In the present study, four of 11 patients with postoperative cognitive impairment did not experience post-CEA hyperperfusion. Thus, cognitive function in these patients might be impaired as a result of other mechanisms, including intraoperative hemispheric cerebral ischemia or microemboli. There were more neuropsychological test scores that displayed a deficit at the 1-month follow-up examination in patients with post-CEA hyperperfusion than in those without hyperperfusion. In addition, although most patients with asymptomatic hyperperfusion or without post-CEA hyperperfusion did not exhibit cognitive impairment at the 6-month postoperative examination, all patients with hyperperfusion syndrome remained cognitively impaired at the 6-month follow up, and this cognitive impairment was associated with deteriorations in their quality of life. These findings indicate that post-CEA hyperperfusion is associated with more global impairments in cognitive function, and the development of hyperperfusion syndrome is associated with prolongation of clinically evident cognitive impairment (that is, ≥6 months after surgery) even if ICH due to hyperperfusion has not occurred.

Carotid artery angioplasty with stent placement has been proposed as an alternative technique for revascularization in cases of ICA stenosis. Authors of previous studies have reported that the incidence of cerebral hyperperfusion syndrome and intracranial hemorrhage following the procedure is between 5 and 6.8% and 1.4 and 4.5%, respectively, rates higher than those in the present study. In contrast, Crawley, et al. have reported that 25% of patients undergoing CA angioplasty exhibited postoperative cognitive impairment and that this incidence was almost equal to that in patients undergoing CEA. Thus, the factors that play a significant role in the development of postoperative cognitive impairment in patients undergoing CA angioplasty remain to be determined.

Conclusions

Impaired cognition leads to deficits in various areas contributing to overall quality of life, that is, work, leisure, and social relations. In the present study we demonstrated that postoperative cerebral hyperperfusion, even when asymptomatic, is associated with impairment of cognitive function in patients undergoing CEA. Although strict control of blood pressure during the postoperative period is effective in preventing ICH due to hyperperfusion, it cannot prevent development of cerebral hyperperfusion itself. Further research regarding strategies designed to decrease the incidence of cognitive impairment associated with post-CEA hyperperfusion would be beneficial.

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