Prediction and monitoring of cerebral hyperperfusion after carotid endarterectomy by using single-photon emission computerized tomography scanning

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Object. The purpose of this study was to determine whether the preoperative measurement of acetazolamide-induced changes in cerebral blood flow (CBF), which is performed using single-photon emission computerized tomography (SPECT) scanning, can be used to identify patients at risk for hyperperfusion following carotid endarterectomy (CEA). In addition, the authors investigated whether monitoring of CBF with SPECT scanning after CEA can be used to identify patients at risk for hyperperfusion syndrome.

Methods. Cerebral blood flow and cerebrovascular reactivity (CVR) to acetazolamide were measured before CEA in 51 patients with ipsilateral internal carotid artery stenosis (≥ 70% stenosis). Cerebral blood flow was also measured immediately after CEA and on the 3rd postoperative day.

Hyperperfusion (an increase in CBF of ≥ 100% compared with preoperative values) was observed immediately after CEA in eight of 12 patients with reduced preoperative CVR. Reduced preoperative CVR was the only significant independent predictor of post-CEA hyperperfusion. Forty-three patients in whom hyperperfusion was not detected immediately after CEA did not exhibit hyperperfusion on the 3rd postoperative day and did not experience hyperperfusion syndrome. In two of eight patients in whom hyperperfusion occurred immediately after CEA, CBF progressively increased and hyperperfusion syndrome developed, but intracerebral hemorrhage did not occur. In the remaining six of eight patients in whom hyperperfusion was detected immediately after CEA, the CBF progressively decreased and the hyperperfusion resolved by the 3rd postoperative day.

Conclusions. Preoperative measurement of acetazolamide-induced changes in CBF, which is performed using SPECT scanning, can be used to identify patients at risk for hyperperfusion after CEA. In addition, post-CEA monitoring of CBF performed using SPECT scanning results in the timely and reliable identification of patients at risk for hyperperfusion syndrome.

KEY WORDS • carotid endarterectomy • single-photon emission computerized tomography • hyperperfusion • cerebrovascular reactivity

Most complications following CEA are ischemic in nature and are due to either embolization or inadequate cerebral protection in patients with a poor collateral blood supply. Nevertheless, postoperative neurological dysfunction may also be related to cerebral hyperperfusion, which is defined as a major increase in ipsilateral CBF that far exceeds the metabolic demands of brain tissue following removal of carotid stenosis. Risk factors for this syndrome include long-standing hypertension, high-grade stenosis, poor collateral blood flow, and contralateral CA occlusion, which often impairs the cerebral hemodynamic reserve. A rapid restoration of normal perfusion pressure after CEA may cause 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 is characterized by a unilateral headache, face and eye pain, seizures, and focal symptoms related to cerebral edema or ICH. The prognosis for patients with ICH is poor, but the incidence of this condition is relatively low (0.4–1.8%). Because strict control of blood pressure during the postoperative period may be effective in preventing ICH, preoperative prediction and early postoperative detection of hyperperfusion is critical for optimizing patient outcomes.

Single-photon emission computerized tomography scanning has been widely used to assess regional brain perfusion, and it can also be used to quantify regional CBF and regional cerebral hemodynamic reserve by measuring the patient’s CVR to acetazolamide.

The purpose of the present study was to determine whether an assessment of changes in preoperative acetazolamide-induced CBF made using SPECT scanning can identify patients at risk for hyperperfusion after CEA. In addition, we wished to assess whether post-CEA CBF monitoring with the aid of SPECT scanning can identify patients at risk for hyperperfusion syndrome.
Prediction and monitoring of hyperperfusion after CEA

Clinical Material and Methods

Patient Population

Between May 1997 and October 1999, 55 patients with ipsilateral ICA stenosis (≥ 70% stenosis) and useful residual function (modified Rankin Scale Score 0, 1, or 2) underwent CEA consecutively. Of 55 patients, 51 entered the present study, whereas four who underwent a CEA in combination with coronary bypass surgery were excluded.

Forty-four of the 51 patients were men and seven were women. The mean age of the patients was 68.2 ± 5.9 years (mean ± SD) and their ages ranged from 50 to 78 years. Concomitant disease states and symptoms were recorded; 38 patients had hypertension, 15 had diabetes mellitus, 18 had coronary artery disease, and 10 patients had lower-extremity atherosclerotic occlusive disease. Twenty-seven patients evinced ipsilateral CA territory symptoms: eight patients experienced TIs, five experienced TIs and a subsequent stroke, and 14 patients suffered a stroke alone. Twenty-four patients had asymptomatic ICA stenosis.

Preoperative MR imaging demonstrated infarction in the hemisphere ipsilateral to the ICA stenosis in 26 patients and no infarction in 25 patients. Twenty-three patients experienced symptomatic infarction with a TIA and/or stroke, whereas the remaining three patients experienced asymptomatic infarction.

All patients underwent preoperative angiography with arterial catheterization. Overall the mean degree of ICA stenosis was 83.8 ± 8.9%, with a range of 70 to 99%, as measured according to the method outlined by the North American Symptomatic Carotid Endarterectomy Trial.20 The contralateral ICA was occluded in four patients and in 12 additional patients there was 60 to 99% stenosis.

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

Cerebral Blood Flow Measurements

Cerebral blood flow was assessed using 123I-IMP SPECT scanning, which was performed with the aid of a ring-type scanner (Headtome-SET 080; Shimadzu Corp., Kyoto, Japan) before CEA and both immediately and 3 days after the procedure. Cerebrovascular reactivity to acetazolamide was also measured for evaluation of the patient’s cerebral hemodynamic reserve before CEA. The preoperative 123I-IMP SPECT study was performed longer than 1 month after the last ischemic event and 7 to 10 days before the CEA.

The 123I-IMP SPECT study was performed with an acetazolamide challenge as described previously,21 and the CBF images were calculated according to the 123I-IMP–autoradiography method.9,10,21 One tomographic plane, where the asymmetry of regional CBF was most prominent, was analyzed for each patient, and the ROI was placed directly on each selected SPECT scan. Following the atlas developed by Kretschmann and Weinrich,13 an irregular ROI measuring 16 cm² or greater was manually drawn in the cerebral cortex perfused by the ipsilateral middle cerebral artery. This ROI was placed in regions where infarction was not present on MR imaging. Identical ROIs were analyzed in each patient or healthy volunteer for all SPECT studies.

The preoperative CVR to acetazolamide was calculated as follows:21 CVR (%) = [(CBF measured after the acetazolamide challenge − resting CBF)/resting CBF] × 100.

Using the 123I-IMP–autoradiography method, 10 healthy volunteers (eight men and two women) between 35 and 65 years of age (mean 52.3 years) were studied to obtain control values.21 The control values of CBF at the resting state and the control CVR were 35.9 ± 4.4 ml/100 g/min and 36.8 ± 9.2%, respectively. When the value of CVR was less than the mean minus two SDs (that is, 18.4%), it was deemed a reduced CVR. Hyperperfusion after CEA was defined as an increase in CBF of at least 100% (that is, a doubling) compared with preoperative values, according to Piepras and colleagues.26

Intraoperative and Postoperative Treatment of Patients

All patients underwent CEA while in a state of general anesthesia more than 1 month after the last ischemic event. Patients were artificially ventilated with an air–oxygen mixture (inspired fraction of oxygen ~ 0.3). Periodic analysis of arterial blood gas samples ensured normoventilation (4.7–5.2 kPa). Blood pressure was maintained within 20% of the preoperative level throughout the procedure by adjusting the depth of anesthesia or, if needed, by intravenous administration of a vasodilator (nicardipine) or a vasoconstrictor (theodrenaline). After induction of anesthesia, a continuous 16-channel electroencephalography tracing was initiated for detection of cerebral ischemia and TCD ultrasound monitoring was performed for detection of microemboli.

An intraluminal shunt and patch grafts were not used in these procedures. The mean duration of ICA clamping was 32 minutes, ranging from 17 to 45 minutes. A drip infusion of 20% mannitol (500 ml) and phenytoin (500 mg) for neuroprotection and a bolus of heparin (5000 U) were administered before the ICA was clamped; protamine sulfate was given at the conclusion of the CEA.

In patients in whom post-CEA hyperperfusion was detected, arterial blood pressure was closely monitored and strictly controlled between 100 and 140 mm Hg by administering intravenous nicardipine while the patient was in the intensive care unit. After the CBF decreased and the hyperperfusion resolved on the 3rd postoperative day, pharmacological control of blood pressure was discontinued. If the hyperperfusion persisted, however, systolic arterial blood pressure was maintained below 90 mm Hg. A diagnosis of hyperperfusion syndrome required the following symptoms: 1) seizure, deterioration of consciousness level, and/or development of focal neurological signs such as motor weakness; and 2) hyperperfusion measured by SPECT scanning after CEA without findings of an additional ischemic lesion on postoperative CT scanning or MR imaging. When hyperperfusion syndrome was identified, a barbiturate coma was induced.

Statistical Analysis

Descriptive statistics are expressed as means ± SDs. Logistic regression analysis was performed to determine the joint effect of multiple variables on hyperperfusion immediately after CEA. Covariates included patient age, sex, complications (hypertension and diabetes mellitus), presence of a symptomatic lesion, infarction on MR imaging, presence of bilateral lesions, the degree of ICA stenosis, the duration of ICA cross-clamping, and CVR. Differences were deemed statistically significant if the probability value was less than 0.05.
Results

All patients recovered within 1 hour after surgery without any new major neurological deficit. There were no additional ischemic lesions on CT scans or MR images obtained on the 1st postoperative day.

Preoperative CVR and Hyperperfusion Immediately After CEA

Ipsilateral hyperperfusion was observed post-CEA in eight (67%) of 12 patients in whom the preoperative CVR had been reduced. Hyperperfusion was not observed post-CEA in 39 patients in whom the preoperative CVR had been normal. A logistic regression analysis demonstrated that decreased CVR was the only significant independent predictor of hyperperfusion immediately post-CEA (Table 1).

Changes in CBF After CEA and Hyperperfusion Syndrome

In 43 patients in whom hyperperfusion was not detected post-CEA there was no development of hyperperfusion or hyperperfusion syndrome for the remainder of the study (Fig. 1). In two (25%) of eight patients in whom hyperperfusion was detected post-CEA, however, there was a progressive increase in CBF (Fig. 2) and development of hyperperfusion syndrome, despite the fact that the systolic arterial blood pressure had been maintained below 90 mm Hg. One of these two patients experienced a focal seizure, as evidenced by motor disturbances of the right upper extremity 6 days after surgery. The other patient experienced confusion and left motor weakness on the 5th postoperative day (Fig. 3). Barbiturate coma was induced in both patients. In the latter patient hyperintense lesions were observed on MR imaging in the region corresponding with hyperperfusion (Fig. 4), whereas in the former patient no lesion was identified. Following termination of the barbiturate coma, both patients eventually experienced a full recovery. Of the eight patients who had post-CEA hyperperfusion, one patient with preexisting lower-extremity atherosclerotic occlusive disease experienced increased pain and cyanosis in the lower extremities on the 2nd postoperative day. After resolution of the hyperperfusion had been confirmed on the 3rd postoperative day, pharmacological control of blood pressure was discontinued, in accordance with the protocol, and the patient’s symptoms improved as blood pressure returned to the preoperative level. Another patient with asymptomatic stenosis of the contralateral ICA (99%) experienced a TIA related to that lesion on the 3rd postoperative day. Immediately after the TIA SPECT scanning was performed and demonstrated disappearance of hyperperfusion in the hemisphere ipsilateral to the site of the CEA and hyperperfusion in the contralateral hemisphere (Fig. 5). After discontinuation of pharmacological control of blood pressure, further ischemic events did not occur.

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**TABLE 1**

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<td>CVR (%)*</td>
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*Values are expressed as means ± SDs. Abbreviation: NS = not significant.

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Fig. 1. Graph depicting increases in CBF after CEA in 43 patients without hyperperfusion. The postoperative CBF increase is expressed as a percentage of the preoperative CBF. These patients did not experience hyperperfusion or the development of hyperperfusion syndrome for the duration of the study. The horizontal dashed line indicates a CBF increase of 100%, which is the definition of hyperperfusion.

Fig. 2. Graph depicting postoperative CBF increases as percentages of preoperative CBF values in eight patients with hyperperfusion immediately after CEA. Arrows indicate two patients in whom hyperperfusion syndrome developed.
prediction and monitoring of hyperperfusion after CEA

Discussion

The present study has demonstrated that performing 123I-IMP SPECT scanning to obtain preoperative measurements of acetazolamide-induced changes in CBF can identify patients at risk for hyperperfusion after CEA. Monitoring of CBF by using SPECT scanning after CEA results in the timely and reliable identification of patients at risk for hyperperfusion syndrome.

Preoperative CVR and Post-CEA Hyperperfusion

Investigators have proposed mechanisms for the development of post-CEA hyperperfusion. In cases in which there is severe ICA stenosis and a deficient collateral blood circulation, hemispheric perfusion pressure is severely reduced distal to the ICA stenosis. This may result in a reduction of perfusion pressure below the compensatory capacity of autoregulatory mechanisms, thus leading to maximal dilation of resistance vessels and chronic hypoperfusion or “misery perfusion.” After restoration of normal perfusion pressure following CEA, chronically impaired autoregulatory mechanisms may require several days to adjust to the new steady state, resulting in hyperperfusion in the interim.

The present study has shown that postoperative hyper-

FIG. 3. Four SPECT scans obtained in a 70-year-old woman with symptomatic stenosis (95%) of the right ICA in whom hyperperfusion syndrome appeared after CEA. Preoperative (preope.) scan obtained at rest (upper left) and after the acetazolamide challenge (lower left) demonstrating poor acetazolamide-induced increases in right middle cerebral artery perfusion. Hyperperfusion is observed on a scan obtained immediately after CEA (center). A scan obtained on the 3rd postoperative day demonstrates worsening hyperperfusion (right). This patient experienced confusion and left motor weakness 5 days after surgery.

FIG. 4. Magnetic resonance T2-weighted images obtained in the same patient as Fig. 3. Preoperative image revealing multiple infarctions in the cerebral white matter (left). Immediately after onset of hyperperfusion syndrome, hyperintense lesions can be seen in the region corresponding to the hyperperfusion observed on SPECT scans (center). On the 28th postoperative day an image demonstrates complete recovery of signal changes in the right cerebral hemisphere (right).
perfusion was observed only in patients with reduced preoperative CVR, which is consistent with previous reports. In addition, our results clearly demonstrate that decreased CVR was a significant independent predictor of post-CEA hyperperfusion. Preoperative measurement of CBF by using an acetazolamide challenge can be used to identify patients at risk for post-CEA hyperperfusion. This supports the theory that hyperperfusion results from a loss of normal vasoconstriction caused by chronic cerebral ischaemia and maladaptive autoregulatory mechanisms.

Cerebral Blood Flow After CEA and Hyperperfusion Syndrome

In the present study, patients in whom there was no immediate post-CEA hyperperfusion did not exhibit hyperperfusion or hyperperfusion syndrome during the duration of the study. In contrast, in two of eight patients with hyperperfusion post-CEA, there were progressive increases in CBF and the development of hyperperfusion syndrome. In the remaining six of eight patients with immediate post-CEA hyperperfusion, the CBF decreased and the hyperperfusion resolved by the 3rd postoperative day. A previous study in which intraoperative TCD ultrasonography was used demonstrated that 11% of patients with post-CEA hyperperfusion later experienced hyperperfusion syndrome, which is consistent with findings from the present study.

Studies conducted by Hosoda and associates and by Yoshimoto, et al. demonstrated that all patients with hyperperfusion that appeared after CEA and persisted between 1 and 5 days postoperatively later experienced hyperperfusion syndrome. In our two patients with hyperperfusion on the 3rd postoperative day, hyperperfusion syndrome developed 5 or 6 days after CEA. Thus, persistence of hyperperfusion longer than several days was associated with the development of hyperperfusion syndrome. Most authors have reported that signs or symptoms of hyperperfusion occur between 3 and 8 days after CEA. In addition, Henderson, et al., demonstrated that hemorrhage due to hyperperfusion occurred between 3 and 8 days after CEA. We therefore advocate the use of SPECT scanning between the 1st and 3rd postoperative day for the timely and reliable identification of patients at risk for hyperperfusion syndrome.

Management of Blood Pressure After CEA

Most authors recommend strict control of blood pressure during the postoperative period to prevent hyperperfusion syndrome. In the present study, two patients experienced hyperperfusion syndrome despite early and strict control of blood pressure. Dalman and associates reported that, although 11% of patients with post-CEA hyperperfusion were symptomatic despite aggressive control of blood pressure, none experienced ICH. This contrasts with the 2% incidence of ICH in patients who underwent CEA without aggressive postoperative control of blood pressure. These data are consistent with our findings.

Carotid artery disease and other vascular atherosclerotic diseases, such as coronary artery disease or lower-extremity atherosclerotic occlusive disease, have similar risk factors and often coexist. In fact, 18 (35%) of our 51 pa-

Fig. 5. Four SPECT scans obtained in a 71-year-old man with symptomatic stenosis (95%) of the left ICA and asymptomatic stenosis (99%) of the right ICA. Preoperative scans obtained at rest (upper left) and after the acetazolamide challenge (lower left) demonstrating poor acetazolamide-induced increases in left middle cerebral artery perfusion. Hyperperfusion is observed on scans immediately after left CEA (center). This patient experienced a TIA with left motor weakness on the 3rd postoperative day. Immediately after the TIA a scan demonstrates resolution of the hyperperfusion in the left hemisphere and hypoperfusion in the right hemisphere (right).
Prediction and monitoring of hyperperfusion after CEA

tients had coronary artery disease and 10 (20%) had lower-extremity atherosclerotic occlusive disease. Additionally, 16 patients (31%) had bilateral CA disease. In the present study, two of eight patients with post-CEA hyperperfusion experienced an ischemic event involving other atherosclerotic stenoocclusive lesions, which was likely caused by relative hypotension experienced while undergoing aggressive therapy to control blood pressure. Thus, in patients with concomitant vascular atherosclerotic disease, post-CEA CBF measurement should aid in the decisions of who should receive aggressive therapy to control blood pressure to minimize the risk of relative hypotension in these patients. In the two patients who experienced ischemic events, aggressive control of blood pressure was discontinued following resolution of hyperperfusion, as demonstrated by SPECT scanning, and the symptoms caused by ischemia resolved. Thus, CBF measurements can also determine the appropriate withdrawal of blood pressure control in patients with ischemic events that are related to other atherosclerotic stenoocclusive lesions.

Limitations of the Present Study

There are several limitations of this study that require discussion. First, all patients underwent CEA performed without an intraluminal shunt. Autoregulation may be impaired as a result of cerebral ischemia during ICA clamping, with subsequent development of hyperperfusion following CEA. Nevertheless, logistic regression analysis demonstrated that the duration of ICA clamping was not a significant independent predictor of hyperperfusion immediately after CEA.

Second, blood pressure was controlled by intravenous administration of nicardipine in patients with hyperperfusion. Nicardipine, which is a calcium-channel blocker, produces a major cerebral vasodilatory activity and increases the CBF. Therefore, nicardipine may exacerbate hyperperfusion. To prevent adverse effects on CBF, Dalman and associates have recommended the use of clonidine or labetalol as an antihypertension drug for hyperperfusion, because neither causes central vasodilation.

Last, SPECT scanning involves substantial costs and technical complexity, and the clinical availability of this method is therefore limited. Recently, it was demonstrated that intraoperative TCD ultrasonography monitoring can be used to identify patients at risk for hyperperfusion and that preoperatively TCD ultrasonography can assess CVR by using an acetazolamide challenge. Furthermore, TCD ultrasonography has the added advantage of providing information regarding the time course of hyperperfusion by using repeated observations. In comparison with SPECT scanning, however, TCD ultrasonography may yield greater false-negative results. In addition, approximately 10% of studies in which TCD ultrasonography is used fail to detect signals of cerebral arterial blood flow due to poor insonation of the cranial window. Thus, SPECT scanning may still be the preferred method.

Conclusions

Although the patient cohort in this study was quite limited, we demonstrated that preoperative measurement of acetazolamide-induced changes in CBF with SPECT scanning can identify patients at risk for hyperperfusion after CEA. In addition, post-CEA CBF monitoring provided the timely and reliable identification of patients at risk for hyperperfusion syndrome. Finally, CBF measurements conducted before and after CEA may assist in the proper management of blood pressure postoperatively.

References


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