Prediction of Cerebral Hyperperfusion after Carotid Endarterectomy Using Cerebral Blood Volume Measured by Perfusion-Weighted MR Imaging Compared with Single-Photon Emission CT


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Cerebral hyperperfusion after carotid endarterectomy (CEA) is defined as a major increase in ipsilateral cerebral blood flow (CBF) following surgical repair of carotid stenosis that is well above the metabolic demands of the brain tissue. Cerebral hyperperfusion syndrome following CEA is a complication of cerebral hyperperfusion that is characterized by unilateral headache, face and eye pain, seizure, and focal symptoms that occur secondary to cerebral edema or intracerebral hemorrhage. Although the incidence of intracerebral hemorrhage is relatively low (0.4%-1.8%), the prognosis for patients with this condition is poor. In addition, a recent study has demonstrated that postoperative cerebral hyperperfusion, even when asymptomatic, is associated with impairment of cognitive function in patients who have undergone CEA.

Risk factors for cerebral hyperperfusion include long-standing hypertension, high-grade stenosis, poor collateral blood flow, and contralateral carotid occlusion, which often result in impairments in cerebral hemodynamic reserve. Furthermore, a rapid restoration of normal perfusion pressure following CEA may result in hyperperfusion in regions of the brain in which autoregulation is impaired due to chronic ischemia. This hypothesis is similar to the “normal perfusion pressure breakthrough” theory described by Spetzler et al and is consistent with observations by several investigators that decreased cerebrovascular reactivity to acetazolamide is a significant predictor of post-CEA hyperperfusion.

The purpose of this study was to determine whether preoperative cerebral blood volume (CBV) measured by perfusion-weighted MR imaging (PWI) could identify patients at risk for cerebral hyperperfusion after CEA.

**Materials and Methods**

**Patients**

Seventy patients with unilateral internal carotid artery (ICA) stenosis (≥70%) and useful residual function (modified Rankin Scale: 0, 1, or 2) undergoing CEA were enrolled in the present study. Sixty of the 70 patients were men. Population age was 69.0 ± 6.8 years (mean ± SD), with a range of 48–78 years of age. Concomitant disease states and symptoms were recorded, including 54 patients with hypertension. Forty-six patients showed ischemic symptoms in the ipsilateral carotid territory, and 24 patients exhibited asymptomatic ICA stenosis. All patients underwent preoperative angiography with arterial catheterization. The overall average degree of ICA stenosis was 82.6 ± 7.9%, with a range of 70%-95%, as per the North American Symp-
CBV Measurements by PWI

CBV measurements, which were obtained by PWI with a Signa 3T imager (GE Healthcare, Milwaukee, Wis) and a standard head coil, were performed as described previously. A spin-echo–type echo-planar imaging sequence was used for PWI with a TR of 1,500 ms, TE of 30 ms, FOV of 240 mm, section thickness of 7 mm, and a 128 × 128 matrix. Sixty images were obtained for each of the 7 sections. In all experiments, 12 mL of gadodiamide (Gd-DTPA-BMA; Omniscan, Nycomed Imaging, Oslo, Norway) was administered at a rate of 3 mL/s, followed by 20 mL of saline flush by using an MR-compatible power injector. The total imaging time was 90 seconds after initiation of the bolus injection.

PWI data were transferred to a postprocessing workstation and analyzed by using the image analysis software system Dr. View (Asahi Kasei, Tokyo, Japan). Quantitative PWI CBV and CBF maps were generated as previously described. The arterial input function was obtained manually from the MCA contralateral to the CEA for deconvolution analysis. In each of the image sections, 1 large irregular region of interest was manually and bilaterally drawn in the cerebral cortex perfused by the MCA (Fig 1), as per the atlas developed by Kretschmann and Weinrich, and the CBF was calculated according to the IMP autoradiography method. In each image section obtained preoperatively and postoperatively, 1 large irregular region of interest was manually drawn in the cerebral cortex perfused by the MCA (Fig 1B), as per the atlas developed by Kretschmann and Weinrich, and the CBF was determined in each region of interest. These regions of interests were placed in regions in which infarction was not present, as confirmed by T1-, T2-, or diffusion-weighted MR imaging.

Post-CEA hyperperfusion was defined as a CBV increase of ≥100% (ie, a doubling) compared with preoperative values, according to Piepras et al.

Preoperative MR imaging including T1-, T2-, diffusion-weighted, and PW sequences and SPECT were performed more than 1 month after the last ischemic event and 7–10 days before CEA.

Intraoperative and Postoperative Management

All patients underwent surgery under general anesthesia more than 1 month after the last ischemic event. Patients were premedicated with midazolam (7.5 mg orally). Anesthesia was induced with fentanyl (2–3 μg/kg intravenously), propofol (1.5–3 mg/kg intravenously), and vecuronium (0.1 mg/kg intravenously) and maintained by repeated boluses of fentanyl (1–2 μg/kg intravenously), vecuronium, and 0.4%–1.0% inspired isoflurane. All patients were artificially ventilated with an air-oxygen mixture (inspired fraction of oxygen ∼0.30). Analysis of intermittently drawn arterial blood gas samples ensured normoventilation (4.7–5.2 kPa). Routine monitoring during anesthesia was performed by using standard electrocardiography and placement of an intra-arterial catheter for direct arterial blood pres-
sure measurement, pulse oximetry, and capnography. Blood pressure was kept stable in a range of ±20% of the preoperative level throughout the procedure by adjusting the depth of anesthesia or, if needed, by intravenous administration of a vasodilator (nitroglycerin) or a vasoconstrictor (theoidrenalin).

An intraluminal shunt was not used in these procedures. The mean duration of ICA clamping was 32 minutes, ranging from 17 to 45 minutes. A bolus of heparin (5000 U) was given before ICA clamping, and protamine was administered at the conclusion of CEA.

All patients underwent CT imaging on the 1st postoperative day and MR imaging including T1- and T2-weighted sequences on the 3rd postoperative day to confirm the presence or absence of additional ischemic lesions.

In all patients with post-CEA hyperperfusion, intensive control of arterial blood pressure between 100 and 140 mm Hg was instituted by using intravenous administration of antihypertensive drugs immediately after SPECT. When CBF decreased and hyperperfusion resolved on the 3rd postoperative day, pharmacologic control of 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 barbiturate coma. A diagnosis of hyperperfusion syndrome had the following requirements: 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 or MR imaging.

**Statistical Analysis**

Descriptive data were expressed as the mean ± SD. Correlations between preoperative CBV or CBF measured by PWI and postoperative CBF increases [(CBF calculated as a percentage of the preoperative value) − 100%] were determined by using linear and polynomial regression analyses and by computing regression equations and correlation coefficients, and the function of better fit was determined. Logistic regression analysis was used to determine the joint effect of multiple variables on hyperperfusion immediately after CEA. Covariates included age, sex, a history of hypertension, a symptomatic lesion, degree of ICA stenosis, duration of ICA cross clamp, and preoperative CBV and CBF measured by PWI. Differences were deemed statistically significance with *P* < .05.

**Results**

All patients recovered from surgery without developing new major neurologic deficits. Furthermore, patients did not exhibit additional ischemic lesions on postoperative CT and MR imaging.

A significant square correlation was observed between preoperative CBV and the increase in CBF immediately after CEA (*r* = 0.785 and *P* < .0001) (Fig 2). Of the 70 patients studied, 7 patients (10%) met CBF criteria for post-CEA hyperperfusion on the SPECT images obtained immediately after surgery. Although post-CEA hyperperfusion was observed in 7 of 15 patients (47%) with elevated preoperative CBV, none of the patients with normal preoperative CBV (*n* = 55) exhibited post-CEA hyperperfusion. There was a weak linear correlation between preoperative CBF measured by PWI and the increase in CBF immediately after CEA (*r* = −0.324 and *P* = .0063). Preoperative CBF measured by PWI was reduced to the mean −2.3 SD of the control value to the mean −1.8 SD of the control value in the 7 patients with post-CEA hyperperfusion. Logistic regression analysis demonstrated that elevated preoperative CBV was the only significant independent predictor of developing post-CEA hyperperfusion immediately after surgery (Table). Other variables, including preoperative CBF measured by PWI, demonstrated no significant association with post-CEA hyperperfusion.

Figure 3 shows the relationship between preoperative CBV, preoperative CBF ratio, and post-CEA hyperperfusion. Although post-CEA hyperperfusion was observed in 7 of 10 patients (70%) with elevated preoperative CBV and elevated preoperative CBF ratio, none of the patients with a combination of elevated preoperative CBV and normal preoperative CBF ratio developed post-CEA hyperperfusion.

In 5 of 7 patients with post-CEA hyperperfusion immediately after surgery, hyperperfusion was not present on the SPECT performed on the 3rd postoperative day, and these 5 patients had uneventful postoperative courses. However, the remaining 2 patients with cerebral hyperperfusion immediately after CEA experienced a progressive increase in CBF on the 3rd postoperative day and developed hyperperfusion syndrome. One of these 2 patients experienced a focal seizure as evidenced by motor disturbances of the right upper extremity 5 days after surgery. The other patient experienced confusion and left motor weakness on the 5th postoperative day. Propofol coma was induced in both patients. The preoperative CBV image obtained by PWI and the pre- and postoperative CBV images obtained by SPECT for 1 of these patients are illustrated in Fig 4. Following termination of the propofol coma, both patients eventually experienced full recovery. The preoperative CBV and CBF ratio mean values of the 2 patients who developed cerebral hyperperfusion syndrome were not significantly different from those values in the other 5 patients with cerebral hyperperfusion on SPECT images obtained immediately after surgery (Fig 2).

**Discussion**

The present study demonstrated that preoperative CBV measured by PWI might help to identify patients at risk for cerebral hyperperfusion after CEA.
<table>
<thead>
<tr>
<th>Variables</th>
<th>Hyperperfusion</th>
<th>No (n = 63)</th>
<th>Odds ratio</th>
<th>95% confidential limits</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr) (mean ± SD)</td>
<td>71.3 ± 3.0</td>
<td>68.7 ± 7.1</td>
<td>1.002</td>
<td>0.692–1.453</td>
<td>0.9904</td>
</tr>
<tr>
<td>Female sex</td>
<td>0</td>
<td>10</td>
<td>0.041</td>
<td>0.001–2.921</td>
<td>0.3259</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0</td>
<td>49</td>
<td>1.323</td>
<td>0.004–483.091</td>
<td>0.9359</td>
</tr>
<tr>
<td>Symptomatic lesion</td>
<td>4</td>
<td>42</td>
<td>0.691</td>
<td>0.394–1.241</td>
<td>0.2159</td>
</tr>
<tr>
<td>Degree of ICA stenosis (%) (mean ± SD)</td>
<td>86.4 ± 4.9</td>
<td>82.1 ± 8.1</td>
<td>1.241</td>
<td>0.884–1.742</td>
<td>0.2129</td>
</tr>
<tr>
<td>Duration of ICA clamping (min) (mean ± SD)</td>
<td>34.7 ± 3.5</td>
<td>32.1 ± 6.2</td>
<td>1.241</td>
<td>0.884–1.742</td>
<td>0.2129</td>
</tr>
<tr>
<td>Preoperative CBF (mL/min per 100 g) (mean ± SD)</td>
<td>19.3 ± 2.5</td>
<td>26.8 ± 8.6</td>
<td>0.691</td>
<td>0.394–1.241</td>
<td>0.2159</td>
</tr>
<tr>
<td>Preoperative CBV (mL/min per 100 g) (mean ± SD)</td>
<td>7.3 ± 0.5</td>
<td>4.8 ± 1.3</td>
<td>0.691</td>
<td>0.394–1.241</td>
<td>0.2159</td>
</tr>
</tbody>
</table>

Note: SD indicates standard deviation; ICA, internal carotid artery; CBF, cerebral blood flow; CBV, cerebral blood volume

These findings support the theory that hyperperfusion results from a loss of normal vasoconstriction secondary to chronic dilation of resistance vessels and maladaptive autoregulatory mechanisms.

In the present study, although post-CEA hyperperfusion was not observed in patients with normal preoperative CBV, patients with elevated preoperative CBV did not always develop post-CEA hyperperfusion. The incidence of post-CEA hyperperfusion in patients with elevated preoperative CBV was 47%, which was lower than that in patients with reduced preoperative cerebrovascular reactivity to acetazolamide measured by SPECT (67%). However, additional use of the relative CBV value (eg, CBV ratio) allowed PWI to detect hyperperfusion states with a sensitivity equal to that of SPECT with acetazolamide challenge. Thus, when using PWI, one should evaluate the quantitative CBV value, as well as the ipsilateral-contralateral cerebral hemispheric asymmetry in the CBV, for a more accurate prediction of post-CEA hyperperfusion.

Several studies using SPECT have demonstrated that decreased cerebrovascular reactivity to acetazolamide is a significant predictor of post-CEA hyperperfusion. However, whether cerebrovascular reactivity to acetazolamide predicts development of hyperperfusion syndrome with a high positive predictive value remains unclear. In the present study, although hyperperfusion syndrome developed in 2 patients with a higher preoperative CBV compared with patients without hyperperfusion immediately after surgery on SPECT images, the preoperative CBV and CBV ratio mean values in these 2 patients were not significantly different from those values in the other 5 patients with cerebral hyperperfusion on SPECT images immediately after surgery. Thus, it also remains unknown if preoperative CBV can predict who will develop hyperperfusion syndrome among patients with hyperperfusion following carotid endarterectomy.

This study has several limitations. For example, the indicator dilution method with arterial input function enables quantification of hemodynamic states in the context of PWI. The arterial input function is usually obtained from the contralateral MCA in patients with unilateral ICA steno-occlusive disease, and the accurate identification of hemodynamic impairment by using CBV measured by PWI is only feasible in patients with unilateral ICA steno-occlusive disease. The present study also included only patients with unilateral ICA stenosis, and the arterial input function was obtained from the contralateral MCA. However, cerebral hemodynamics are more severely impaired in patients with bilateral ICA steno-occlusive disease than in...
those with unilateral ICA stenosis, and risk factors for cerebral hyperperfusion syndrome after CEA include contralateral carotid steno-occlusive disease. Thus, whether PWI can accurately measure CBV in patients with bilateral ICA steno-occlusive disease or whether the CBV can identify patients at risk for cerebral hyperperfusion after CEA in such patients remains unclear.

Although SPECT with an acetazolamide challenge is a reliable method for identifying patients at risk for cerebral hyperperfusion after CEA, the clinical use of SPECT is precluded by its high cost and limited availability. In addition, acetazolamide is associated with frequent various adverse effects, including metabolic acidosis, hypokalemia, numbness of the extremities, headache, tinnitus, and gastrointestinal disturbances. By contrast, PWI does not require ionizing radiation, and its relatively short scanning time is well suited for clinical MR imaging examinations. Although the use of the 3T MR imager in the present study is less widespread than that of the 1.5T model, CBV has been quantified by using both models. Furthermore, CBV measured by using 1.5 and 3T magnets reportedly correlates with cerebrovascular reactivity to acetazolamide measured by using SPECT and positron-emission tomography, respectively. Thus, CBV measured by using a 1.5T magnet might also identify patients at risk for cerebral hyperperfusion after CEA.

Most investigators recommend strict control of blood pressure in the postoperative period to prevent intracranial hemorrhage due to cerebral hyperperfusion after CEA. On the other hand, 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, and aggressive blood pressure control may induce ischemic events involving the other atherosclerotic steno-occlusive lesions. Thus, identifying patients at risk for post-CEA hyperperfusion may result in appropriate induction of postoperative blood pressure control to minimize the risk of the relative hypotension.

**Conclusion**

The present study demonstrated that preoperative CBV measurements by PWI might help to identify patients without contralateral ICA steno-occlusive disease who are at risk for cerebral hyperperfusion after CEA.

**References**


