Acetazolamide-Challenged Brain CT Perfusion before and after Carotid Stenting

Ho Sung Kim, MD, Eun Jin Kim, MD, Sun Yong Kim, MD

**Purpose:** To test hypothesis that pre-stenting measurement of reactivity index by using acetazolamide-challenged CT perfusion could identify patients at risk for hyperperfusion after carotid stenting.

**Materials and Methods:** For 24 regions of interest in 12 patients with symptomatic unilateral high-grade carotid stenosis, asymmetric indexes for cerebral blood volume, cerebral blood flow, and mean transit time and reactivity index were calculated from resting and acetazolamide-challenged CT perfusion before and 1 day after carotid stenting. We subsequently compared pre-stenting asymmetric indexes and reactivity index with percent increase of cerebral blood flow 1 day after carotid stenting.

**Results:** Percent increase of cerebral blood flow on the first post-stenting day was not significantly different between visually decreased and normal cerebrovascular reserve groups. There was no significant correlation between pre-stenting asymmetric indexes of resting CT perfusion parameters and percent increase of cerebral blood flow 1 day after carotid stenting. On the other hand, pre-stenting reduction of reactivity index showed fair correlation with 1 day cerebral blood flow increase. However, hyperperfusion or hyperperfusion syndrome was not observed in any patient with reduced reactivity index.

**Conclusion:** Pre-stenting measurements of resting CT perfusion parameters and reactivity index could not predict hyperperfusion after carotid stenting. However, pre-stenting reduction of reactivity index seems to fairly correlate with immediate post-stenting cerebral blood flow increase. Further studies with larger population should be performed to validate this preliminary result.

**Key Words:** Hyperperfusion; Hyperperfusion syndrome; CT perfusion; Carotid artery stenosis; Stent
For this reason, prediction of hyperperfusion before CS or CEA is important. Previous study proposed that the possible risk factors for hyperperfusion syndrome are hypertension, high-grade carotid stenosis, poor collateral blood flow, and contralateral carotid occlusion (11). It has been reported that the risk of hyperperfusion syndrome increased in patients whose cerebrovascular reactivity were reduced (8, 12). Paired CBF measurements with the initial measurement obtained at rest and the second measurement obtained following a cerebral vasodilatory stimulus to calculate percent changes are intended to detect the presence of autoregulatory vasodilation (13). SPECT has been widely used to assess regional brain perfusion with semiquantitative measurement (1,14). According to Hosoda et al., SPECT with acetazolamide challenge could identify patients at risk for hyperperfusion after carotid endarterectomy. Drug-challenged CT perfusion (CTP) or MRI also can measure cerebrovascular reserve (CVR) in a similar way with SPECT. Although SPECT is an established method for measuring CBF with or without acetazolamide challenge in patients with stroke or carotid disease (15, 16), it usually has to be performed in a two-day setting due to tracer kinetics. Moreover, it provides less morphological information than CT or MRI. PET cannot routinely be applied to patients in many hospitals. The usefulness of dynamic CTP imaging for early diagnosis of acute ischemic stroke has previously been reported, and it has become a promising tool for a quick evaluation of the cerebral circulation in an acute stroke (17, 18). Moreover, this imaging modality is much more readily accessible imaging method to assess cerebral hemodynamic status in patients with cerebral steno-occlusive arterial disease than SPECT and PET. However, 64-channel multidetector CT scanner which overcome limited coverage of brain with using previous CTP was recently developed and so brain CTP can be routinely available only in hospitals with recently purchased CT scanner. The purpose of this study was to test hypothesis that pre-stenting measurement of reactivity index (RI) by using acetazolamide-challenged CTP (ACZ-CTP) could identify patients at risk for hyperperfusion immediately after carotid stenting.

MATERIALS AND METHODS

Study Population

Between August 2006 and September 2008, 23 consecutive patients underwent CS, 12 of whom fulfilled the following inclusion criteria and were enrolled in this study. The inclusion criteria were as follows: digital subtraction angiography (DSA) showing unilateral proximal internal carotid artery (ICA) stenosis with > 70% diameter reduction, no notable renal insufficiency or allergy to contrast agent, and underwent ACZ-CTP before and 1 day after CS. To determine the degree of ICA stenosis, we used the criteria of the North American Symptomatic Carotid Endarterectomy Trial (NASCET) (19). None of the patients had stenosis in intracranial vasculature. There were 7 men (age range, 56–81 years; median age, 66.1 years) and 5 women (age range, 55–74 years; median age, 63.8 years). All study patients had experienced single or recurrent episodes of transient ischemic attack such as hemiparesis or hemihypesthesia. In these patients, the symptoms were referable to the side of the stenosed carotid artery. All patients underwent neurologic and cardiology evaluation, electrocardiography, Doppler sonography, and CT angiography or DSA of the epiaortic vessels and were treated with antiplatelet therapy. The degree of neurological impairment was evaluated with using the National Institute of Health stroke score (NIHSS). Stroke risk factors such as arterial hypertension, generalized arterial occlusive disease and diabetes mellitus were reviewed in all study patients. Our institutional review board approved this study and written informed consent was obtained from every participant in accordance to the guidelines of the institutional review board at our institution.

CT Perfusion Imaging Protocol and Data Processing

Our CT imaging protocol for patients with symptomatic carotid stenosis consisted of nonenhanced CT and ACZ-CTP. CTP studies were performed with using a 64-channel multi-detector CT scanner (Brilliance 64 Channel CT, Philips Medical Systems, Cleveland, Ohio, USA). CTP consisted of a 60 second series with 30 gantry rotations performed in a cine mode during contrast material administration. CTP images were acquired at the level of the basal ganglia covering all 3 vascular territories and consisted of a series of 30 images for each section. A 50 mL bolus of non-ionic contrast media (Omnipaque, iodine 300 mg/mL; Amersham Health, Princeton, NJ, USA) was administered into an antecubital vein by using a power injector with injection rate of 4.5 mL/s and the scanning was initiated 2 seconds after the start of the injection. CT scans were studied once before intravenous infusion of 1000 mg of acetazolamide (ACZ) (Diamox; Wyeth,
Marietta, PA, USA), and again 20 minutes after the infusion of ACZ. Both resting and ACZ-challenged CTP studies were obtained during the same session with patients remaining in supine position.

CTP data were analyzed by using brain perfusion software (Extended Brilliance Workstation v 3.0, Philips Medical Systems, Cleveland, Ohio, USA). The software relies on the central volume principle to calculate perfusion parameters from the time-concentration curve. It has been reported that this principle is the most accurate for low injection rates of iodinated contrast agent (20). The software applies curve fitting by a least-mean-squares method to obtain mathematical descriptions of the time-attenuation curves, and mean transition time (MTT) map was calculated by a noniterative deconvolution operation from the time-concentration curve of a particular voxel and the arterial input function (AIF) (20). An AIF was selected by placing a small circular region of interest within anterior cerebral artery contralateral to affected hemisphere. A venous output function was selected by placing a circular ROI within superior sagittal sinus. For each voxel, the cerebral blood volume (CBV) map was calculated from the areas under the time-concentration curves. The CBF map for each voxel is finally calculated according to the following equation combining CBV and MTT value: CBF = CBV / MTT (21).

**Data Analysis**

For the visual analysis of perfusion parametric maps, all resting and ACZ-challenged CTP maps were scored for relative perfusion abnormalities by using a 20-level color scale. We could visually discriminate more than four color scale difference between the hemispheres. Two experienced neuroradiologists independently and blindly evaluated the CBV, CBF, and MTT maps before and after ACZ injection. For the evaluation of resting parameters, more than four color scale (20%) decrease in each vascular territory ipsilateral to high-grade carotid stenosis compared with normal contralateral hemisphere was defined as visually decreased value of perfusion parameter. A comparison was then made of the relative perfusion changes between the resting and ACZ studies. Cases with a increase less than 20% (four color change) or paradoxically reduction of perfusion in the expected territory of the middle cerebral artery (MCA) and the anterior external border zone (ABZ) on ACZ-CTP maps, compared with the resting CTP maps, were defined as having a visually “decreased CVR group” whereas cases that show a increase more than 20% in perfusion were defined as having a “normal CVR group”. After the blinded study, discrepancies were resolved by consensus. Finally, the consensus data of the CTP images were used in the comparison between the values of CTP parameters before and after CS.

For the quantitative analysis, an experienced neuroradiologist drew standardized polygonal mirrored regions of interest (ROIs) manually on the reference CT image over the cortical gray matter of the expected territory of MCA and ABZ. To eliminate vascular pixels from the calculation and from the color perfusion images, any pixel with the value 9 ml/100 g and greater in the CBV image is not displayed on the perfusion maps or included in the ROI measurement. Removed pixels were colored black (zero value) and those same pixels were also removed from the CBF and MTT maps. From each ROI, the absolute values of the CBF, CBV, and MTT were calculated and then, for normalization of each baseline parameter, asymmetric index (AI) was

<table>
<thead>
<tr>
<th>Number</th>
<th>Sex / Age</th>
<th>Symptom</th>
<th>Risk Factors</th>
<th>Stenosis Degree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M / 81</td>
<td>TIA, Lt side weakness</td>
<td>HTN</td>
<td>80%</td>
</tr>
<tr>
<td>2</td>
<td>F / 74</td>
<td>TIA, Dysarthria,</td>
<td>DM, HTN, CHD</td>
<td>85%</td>
</tr>
<tr>
<td>3</td>
<td>F / 67</td>
<td>TIA, Rt side weakness</td>
<td>DM, HTN</td>
<td>87%</td>
</tr>
<tr>
<td>4</td>
<td>M / 70</td>
<td>TIA, Rt side weakness</td>
<td>DM, HTN, CHD</td>
<td>97%</td>
</tr>
<tr>
<td>5</td>
<td>F / 65</td>
<td>TIA, Lt side weakness</td>
<td>HTN</td>
<td>95%</td>
</tr>
<tr>
<td>6</td>
<td>M / 56</td>
<td>TIA, dysarthria</td>
<td>DM, HTN, CHD</td>
<td>85%</td>
</tr>
<tr>
<td>7</td>
<td>M / 64</td>
<td>TIA, Rt side weakness</td>
<td>DM, HTN</td>
<td>79%</td>
</tr>
<tr>
<td>8</td>
<td>M / 66</td>
<td>TIA, Lt side weakness</td>
<td>HTN, CHD</td>
<td>92%</td>
</tr>
<tr>
<td>9</td>
<td>M / 64</td>
<td>TIA, Rt side weakness</td>
<td>DM, HTN</td>
<td>95%</td>
</tr>
<tr>
<td>10</td>
<td>F / 58</td>
<td>TIA, Lt side weakness</td>
<td>HTN</td>
<td>85%</td>
</tr>
<tr>
<td>11</td>
<td>M / 62</td>
<td>TIA, Rt side weakness</td>
<td>DM, HTN</td>
<td>95%</td>
</tr>
<tr>
<td>12</td>
<td>M / 55</td>
<td>TIA, Rt side weakness</td>
<td>DM, HTN</td>
<td>89%</td>
</tr>
</tbody>
</table>

Note.— TIA = transient ischemic attack; HTN = hypertension; DM = diabetes mellitus; CHD = coronary heart disease.
calculated by dividing the absolute values in the stenotic hemispheres by those in the contralateral normal hemisphere. These AIs of resting parameters were investigated before and 1 day after CS. For the ACZ-CTP study, a section at the same level as the one selected for the baseline study was selected. For the evaluation of vascular reserve capacity, reactivity index (RI) was calculated as follows: \( \text{RI} (\%) = \left( \frac{\text{AI of } \text{CBF}_{\text{Acetazolamide}} - \text{AI of } \text{CBF}_{\text{Baseline}}}{\text{AI of } \text{CBF}_{\text{Baseline}}} \right) \times 100 \), where AI of \( \text{CBF}_{\text{Baseline}} \) and AI of \( \text{CBF}_{\text{Acetazolamide}} \) represented AI of CBF before and after intravenous injection of ACZ, respectively. Percent change of CBF increase 1 day after carotid stenting was calculated as follows: \( \left( \frac{\text{AI of } \text{CBF}_{\text{poststenting}} - \text{AI of } \text{CBF}_{\text{prestenting}}}{\text{AI of } \text{CBF}_{\text{prestenting}}} \right) \times 100 \).

**Statistical analysis**

Interobserver agreement for the quantitative analyses of resting CTP parameters and RI were measured by using intraclass correlation coefficient (ICC). The percent change of CBF increase 1 day after CS were compared between the visually normal and the visually decreased CVR groups in the ABZ and MCA territories by using the Mann-Whitney U test. The correlations between the percent change of CBF increase 1 day after CS and the values of CTP parameters before CS were calculated with using Spearman’s correlation coefficient.

**RESULTS**

**Visual Analysis of CTP Parameters versus 1 Day CBF Increase**

All patients underwent ACZ - CTP successfully. No adverse effects were reported after ACZ administration. On visual analysis, all patients displayed longer MTT ipsilateral to high-grade carotid stenosis, which was most pronounced in ABZ. For resting CBF, there was a

![Fig. 1. The comparison the percent change of cerebral blood flow increase 1 day after carotid stenting between visually normal and abnormal groups of cerebral blood volume (A), cerebral blood flow (B), and cerebrovascular reserve (C) before carotid stenting.](image-url)
trend for slightly lower preoperative values in the symptomatic hemisphere than in contralateral normal hemisphere. The CBV values remained homogeneous between the symptomatic and contralateral normal hemispheres. Among the 24 regions in the territories of MCA and ABZ ipsilateral to carotid stenosis, 15 regions had a visually decreased CVR, with a perfect interobserver agreement ($\kappa = 1.0$). There was no statistically significant difference of percent change of CBF increase 1 day after CS between the visually normal and decreased CVR groups (3.7 ± 5.3% vs. 6.5 ± 11.5%, p > 0.05) (Table 1; Fig. 1). Maximum 1 day CBF increase was observed in the reduced CVR group (42%) (Fig. 2). Hyperperfusion (CBF increase of > 100% compared with baseline values) or hyperperfusion syndrome including intracerebral hemorrhage was not observed in both reduced and normal CVR groups.

**Quantitative Analysis of CTP Parameters versus 1 Day CBF Increase**

On quantitative analysis, ICC for measurement of CTP parameters between the two observers, was excellent (ICC = 0.82). The AIs of resting CTP parameters before stenting were not significantly correlated with the percent change of CBF increase 1 day after CS ($r = -0.06$ for AI of CBV; $r = -0.26$ for AI of CBF; $r = 0.39$ for AI of MTT, p > 0.05) (Fig. 3). The RI before stenting was fairly correlated with the percent change of CBF increase 1 day after CS ($r = -0.58$, 95% confidence interval $-0.81 ~ -0.32$) (Fig. 3).

**DISCUSSION**

The present study showed that the feasibility of performing ACZ-CTP to identifying patients at risk for hyperperfusion after CS is questionable. In this study,
there was no significant correlation of CBF increase on the first post-stenting day with pre-stenting resting CTP parameters including visual and quantitative CBV, CBF, and MTT. None of our patients had hyperperfusion or hyperperfusion syndrome immediately after CS in both reduced and normal CVR groups. On the other hand, the RI obtained by ACZ-CTP before stenting fairly correlated with 1 day CBF increase after CS.

It has been reported that hyperperfusion, which is defined as a 100% increase in ipsilateral CBF, could be a significant risk factor for intracerebral hemorrhage (9). Therefore, prediction and detection of hyperperfusion is important for prevention by strict control of blood pressure (9, 11). Previous CEA studies proposed that preoperative impairment of CVR is a risk factor for hyperperfusion syndrome (1, 12). Another SPECT study also reported that hyperperfusion was observed in 8 of 12 patients with reduced preoperative CVR (15). Previous investigators have proposed that in case in which there are high grade carotid stenosis and an insufficient collateral blood flow, hemispheric perfusion pressure is markedly decreased below the
CVR ranges from 20%–70% hyperperfusion in patients with reduced preoperative namic due to chronic stenosis (2). Incidence of hyperperfusion, in the situation of impaired autoregu-
grade carotid stenosis by CEA was suggested to cause rapid restoration of blood flow after correction of high-
maximal dilatation of resistance vessels (2). Thereafter, thus leading to chronic hypoperfusion status with 
compensatory capacity of autoregulatory mechanisms, 
affected hemisphere, owing to increase of length of the
more dispersion than that on the unaffected or slightly-
AIF on the affected hemisphere will be subjected to 
collateral recruitment. It is reasonable to expect that an 
over the circle of Willis, therefore, are influenced by 
major cerebral vessels for the AIF. These vessels lie 
with CTP, it could also provide additional information 
on the anatomic information and higher spatial resolution. If 
workstation. CTP also provides more accurate 
perfusion maps can be generated in a short time at a 
perfusion syndrome.
functioning in patients with reduced preoperative 
non-diagnostic CTP. CTP commonly leads to the selection of 
some parameters to evaluate cerebral hemodynam-
increase after CS. Moreover, post-stenting hyperperfu-
sion was not seen in the reduced CVR group. However, 
pre-stenting reduction of RI fairly correlated with 1 day 
CBF increase and maximum CBF increase among the 
study patients was found in the reduced CVR group. 
The relatively small sample size may have reduced the 
probability of detecting a statistically significant 
relationship between the values of perfusion parameters obtained by using ACZ-CTP and post-stenting CBF increase.
Perfusion imaging based on CT allows the evaluation of some parameters to evaluate cerebral hemodynamics, such as CBF, CBV and MTT. CTP imaging can be easily performed as with a standard brain CT examination, with a small increase in the time and costs of the imaging technique (23). Also, compared to ACZ-challenged SPECT currently widely performed, which takes at least 2 day for examination, the dynamic CTP is much more readily accessible imaging method to assess cerebral hemodynamic status in patients with cerebral steno-occlusive arterial disease, and its perfusion maps can be generated in a short time at a workstation. CTP also provides more accurate anatomic information and higher spatial resolution. If the CT angiography is performed in the same session with CTP, it could also provide additional information about vascular structure or abnormality.
There are several limitations regarding the quantifica-
tion of CTP. CTP commonly leads to the selection of 
major cerebral vessels for the AIF. These vessels lie 
over the circle of Willis, therefore, are influenced by 
collateral recruitment. It is reasonable to expect that an 
AIF on the affected hemisphere will be subjected to 
more dispersion than that on the unaffected or slightly-
affected hemisphere, owing to increase of length of the 
collateral pathways supplying this region. However, the

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경동맥스텐트설치 전후의 Acetazolamide 부하 뇌관류CT

1 아주대학교병원 영상의학과

김호성 · 김은진 · 김선용

목적: 경동맥 스텐트 설치 전 acetazolamide 부하 뇌관류CT를 이용하여 측정한 반응지수(reactivity index) 값이, 스텰트 설치 후 과관류에 대한 위험도를 예측할 수 있는지에 대해 알아보고자 하였다.

대상 및 방법: 유증상의 일측성 고도 경동맥 혈착증 12명의 환자를 대상으로 24개의 관심영역을 지정하여, 각각에서 경동맥 스텰트 설치 전과 하루 후에 기저 및 acetazolamide 부하 뇌관류CT를 시행하였다. 이를 통해 뇌혈용적(cerebral blood volume), 뇌혈류량(cerebral blood flow, CBF), 평균통과시간(mean transit time)에 대한 비대칭지수(asymmetric index) 및 반응지수를 계산하였고, 경동맥 스텰트 설치 전의 비대칭지수 및 반응지수를 스텰트 설치 1일 후의 CBF 백분율 증가량과 비교하였다.

결과: 시각적으로 뇌혈관예비능이 감소한 집단과 정상인 집단간의 스텰트 설치 후 CBF 백분율 증가량은 유의한 차이를 보이지 않았다. 경동맥 스텰트 설치 전의 기저뇌관류CT 지표들에 대한 비대칭지수와, 스텰트 설치 후의 CBF 백분율 증가량 간에는 유의한 상관관계가 나타나지 않았다. 반면에, 경동맥 스텰트 설치 전의 반응지수 감소량은 스텰트 설치 후의 CBF 백분율 증가량과 유의한 상관관계를 나타냈다. 반응지수가 감소된 환자 중 과관류를 보인 환자는 없었다.

결론: 경동맥 스텰트 설치 전의 뇌관류CT와 반응지수는 스텰트 설치 이후의 과관류를 예측할 수 없었다. 그러나, 스텰트 설치 전의 반응지수 감소량은 스텰트 설치 직후의 CBF 증가와 유의한 상관관계를 보였다.

Key Words : Hyperperfusion; Hyperperfusion syndrome; CT perfusion; Carotid artery stenosis; Stent