Objective evaluation of cerebrovascular reactivity for acetazolamide predicts cerebral hyperperfusion after carotid artery stenting: Comparison with region of interest methods

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Abstract

BACKGROUND AND PURPOSE: Hemodynamic impairments are considered risk factors of cerebral hyperperfusion after carotid artery stenting (CAS); measurement by SPECT using a subjective ROI method lacks consistency and reproducibility.

MATERIALS AND METHODS: The present study compared objective perfusion analysis (stereotactic extraction estimation [SEE] method) with the ROI method for preoperative SPECT to predict the hyperperfusion phenomenon (HPP) after CAS. Preoperative resting asymmetry index (CBF ratio from the affected to unaffected hemisphere) and cerebrovascular reactivity (CVR) to acetazolamide were measured by *N*-isopropyl-p-[^{123}I]-iodoamphetamine SPECT using the SEE and ROI method in 84 patients. CBF was also measured the day after CAS. Perfusion data with the highest area under the curve (AUC) by receiver-operating characteristic (ROC) analysis was considered a perfusion risk factor of HPP. Multivariate analyses for clinical characteristics and perfusion risk factors were performed to determine predictors of HPP.

RESULTS: The HPP was observed in 10 patients (11.9%). Female sex, contralateral stenosis, and degree of stenosis were significantly associated with HPP development on univariate analysis, and symptomatic stenosis was not found to be a significant factor. On SPECT analysis, CVR in the MCA area by SEE method had the highest AUC (0.981). Multivariate analysis showed that CVR in the MCA area was a significant predictor of HPP (p=0.041). To

predict hyperperfusion, the ROC curve of the CVR showed a cutoff value of -0.60%, sensitivity of 94.6%, and specificity of 100% ($p<0.001$).

CONCLUSIONS: Objective SEE method had better a predictive capability than ROI method to identify risk of hyperperfusion after CAS.

Keywords: asymmetry index, carotid artery stenting, cerebrovascular reactivity, hyperperfusion, single-photon emission computed tomography, stereotactic extraction estimation

Introduction

Carotid artery stenting (CAS) has been performed as an alternative to carotid endarterectomy (CEA) for revascularization in cases of carotid artery stenosis in which CEA carries a high risk. Although cerebral infarction and in-stent restenosis were reported as common complications associated with CAS, cerebral hyperperfusion syndrome (HPS) following CAS is a rare but potentially devastating complication that occurs under the conditions of the hyperperfusion phenomenon (HPP) [1-12]. The prognosis of HPS has a poor prognosis, with mortality rates of 36 to 63%, and survivors have significant morbidity [13]. Consistent with reports describing cerebral hyperperfusion after CEA, the reported preoperative risk factors of hyperperfusion after CAS are patient age, asymmetry index (ipsilateral/contralateral resting cerebral blood flow [CBF]), cerebrovascular reactivity (CVR) to acetazolamide, severe internal carotid artery stenosis, contralateral stenosis or occlusion, and periprocedural hypertension [14, 4, 3, 1, 15]. Although previous studies assessed CVR and asymmetry index using SPECT with the ROI method, the ROI method lacks consistency among studies and has poor reproducibility [4, 3, 16]. Conversely, the stereotactic extraction estimation (SEE) method can automatically analyze the brain perfusion data in stereotactic space objectively and reproducibly [16, 17]. Different from the ROI method, the perfusion data using the SEE method were depicted to whole brain surface area, and automatically quantifies the CBF and CVR in each pre-defined region of the anterior cerebral artery (ACA), middle cerebral artery

(MCA), and posterior cerebral artery (PCA) [17]. No reports have compared the objective SEE and ROI method for detection of risk factors of HPP. The present study retrospectively evaluated the strongest risk factor of cerebral hyperperfusion after CAS among SPECT data with both the SEE and ROI method.

Methods

The eligibility criterion was stenosis of the internal carotid artery of more than 50% on digital subtraction angiography in symptomatic patients, and more than 80% in asymptomatic patients. During the study period (January 2007 to December 2015), 106 consecutive patients underwent CAS. Of these, 22 patients were excluded from analysis for the following reasons: emergent CAS without preoperative SPECT (N=5), previous large old cerebral infarction (N=2), staged angioplasty (N=1)[18], subsequent CAS for restenosis after initial CAS (N=1), and lack of preoperative SPECT *N*-isopropyl-p-[^{123}I]-iodoamphetamine (IMP) (N=13). Thus, 84 patients remained for our analysis (73 men and 11 women). The mean age of the patient population was 70.4 ± 7.1 years (range, 52–84 years). The patient characteristics are shown in Table 1.

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

We performed preoperative CBF ^{123}I-IMP SPECT study at rest and with an acetazolamide challenge. CBF SPECT at rest was also performed the following day after CAS. The preoperative CBF SPECT data were obtained using the dual table autoradiography (DT-ARG) method, which was modified from the original autoradiography (ARG) method. The DT-ARG method can acquire CBF SPECT images both at rest and with an acetazolamide challenge in one day [19, 20, 17]. First, patients were administered 111 MBq of ^{123}I-IMP intravenously, while resting CBF SPECT acquisition was started simultaneously. Blood was sampled from the brachial artery 10 min after the injection. Second, for the drug challenge, 15 mg/kg of acetazolamide was injected 20 min after the resting ^{123}I-IMP injection. Finally, 10 min after the acetazolamide injection, 111 MBq of ^{123}I-IMP was administered to the patients and CBF SPECT was acquired for the acetazolamide challenge. The SPECT acquisition time was 28 min for each of the resting and the acetazolamide challenge conditions, and the total examination time was <1 hour. The postoperative CBF imaging was performed using the ARG method, which followed the same protocol as the first step of the preoperative SPECT. All images were obtained by an e-cam dual-headed gamma camera (Siemens Healthcare GmbH, Erlangen, Germany) equipped with low-energy high-resolution fan-beam collimators. Projection data were obtained with a 64 x 64 matrix in 4 min x 7 rotations of 180 degrees from each camera at a sampling step angle of 4 degrees, and with

triple photopeaks for triple energy window (TEW) scatter correction (160 keV, 24% and 134, 172 keV, 3%). Scanning was performed with a transaxial resolution of 9.6 mm in full-width at half-maximum (FWHM).

Each projection image was executed with QSPECT, the automated package software supplied by Nihon Medi-Physics Co., Ltd. (Tokyo, Japan). The DT-ARG algorithm in the software has been described previously; briefly, it is based on the autoradiography method using two look-up tables, and it can acquire CBF data under an acetazolamide challenge just after performing resting CBF [20]. After scatter correction was performed with the TEW method, tomographic images were reconstructed from the 64 x 64 matrix in the transverse plane using an ordered subset expectation maximization algorithm with 3 iterations and 5 subsets. Attenuation correction was performed using the sinogram threshold fitting (estimated skull image by filtered back projection of the reciprocal of an emission sinogram) using the Chang method (0.167 cm^{-1}). After reconstruction, a 7.0-mm FWHM Gaussian post-filter was applied. The reconstructed spatial pixels were 2.85 mm for the x- and y-planes and 3.44 mm for the z-plane. Reconstructed images were translated into quantitative tomographic images from arterial sampling data using the DT-ARG method for the preoperative study and the ARG method for the postoperative study.

For the SEE method, all imaging data was analyzed using a PC running Windows 7 (Microsoft, Redmond, WA). Brain surface images were obtained using the three-dimensional

stereotactic surface projection (3D-SSP) programs. To ensure the correct transfer to the stereotactic brain coordinates, we evaluated the fit of the transferred midsagittal images at rest and for the acetazolamide challenge by superimposing the midsagittal images. The SEE method can show 3D-SSP format view sets of CBF without acetazolamide (Rest CBF), CBF with acetazolamide (acetazolamide CBF), CVR, and staging of hemodynamic ischemia (Figure 1A, B). The borderline of ACA, MCA, and PCA territories were preset on the brain surface image using 3D-SSP programs (Figure 1B). The SEE method evaluated the mean CBF and CVR in the entirety of each territory. CVR and asymmetry index were defined as (acetazolamide CBF - Rest CBF)/Rest CBF×100 (%) and the ipsilateral Rest CBF/contralateral Rest CBF, which were automatically calculated.

For the ROI method, slices at the anterior commissure-posterior commissure level +20 mm of the standardized images was used [21]. In this slice, six ROIs, the ACA, anterior and posterior part of the MCA, anterior and posterior part of the white matter (WM), and PCA, were placed (Figure 1C). Rest CBF, acetazolamide CBF, CVR, and asymmetry index at rest were measured in each area.

Intraoperative and Postoperative Management

Carotid artery angioplasty and stenting were performed by three neurointerventionalists. Dual (aspirin 100 mg and clopidogrel 75 mg) or triple (aspirin 100 mg, clopidogrel 75 mg, and

cilostazol 200 mg) antiplatelet therapy was administered for a minimum of 7 days prior to the procedure. The free radical scavenger edaravone (30 mg) (Tanabe Mitsubishi Parma Co, Tokyo, Japan) was preoperatively administered in all patients to prevent cerebral hyperperfusion [22]. The patients were placed under local anesthesia, and a bolus injection of heparin (80 IU/kg) was given immediately before the intervention to increase the activated clotting time to a minimum of 250 seconds. A 6 French, 90 cm catheter sheath was inserted from the femoral or brachial artery to the ipsilateral common carotid artery. We used Angioguard (Johnson & Johnson, Cordis, Minneapolis, MN, USA), FilterWire (Boston Scientific, Natick, MA, USA), or GuardWire (Medtronic, Santa Rosa, CA, USA) as the embolic protection device for all patients. All but 7 patients underwent predilation of the internal carotid lesions using a 3.5-mm balloon catheter protected with the embolic protection device. Precise (Johnson & Johnson, Cordis) and Wallstent RP (Boston Scientific) were used in 40 and 44 patients, respectively. Postdilation was performed in 70 patients with a 4.5- or 5.0-mm balloon catheter with 6-atm inflation pressure. In cases with insufficient stent expansion, the balloon was further inflated to 10 atm.

HPP was defined as an asymmetry index of more than 1.20 compared with the normal side on SPECT the day after CAS [18, 23]. HPS was defined as a neurological deficit that occurred after cerebral revascularization, was localized ipsilateral to the treated artery, and was not related to thromboembolism.

Statistical Analysis

Data are presented as the mean ± standard deviation. Statistical analysis was performed using SPSS (version 23.0 for Windows; SPSS Inc, Chicago, IL). We used Fisher's exact test and the $\chi 2$ test for categorical variables. The association between HPP and continuous variables was estimated by calculating odds ratios (OR) with 95% confidence intervals (CIs), using binary logistic regression models. For SPECT data, the factor which had the highest value of the area under the curve (AUC) on receiver-operating characteristic (ROC) curve analyses was considered as the strongest risk factor of HPP. On multivariate analysis, the models were adjusted for variables with $P<0.05$ in the univariate analyses and the strongest risk factor of SPECT data.

Results

The baseline characteristics of the patients are shown in Table 1. Among 84 patients, 73 (86.9%) were men and 11 (13.1%) were women, and their mean age was 70.4 ± 7.1 years. The overall average degree of ICA stenosis was 74.8 ± 17.6% (range, 52%–95%) according to the method of the North American Symptomatic Carotid Endarterectomy Trial [24]. CAS was performed without neurological deterioration in all but two patients who suffered minor cerebral infarction in the affected MCA area with mild hemiparesis.

Ten patients (11.9%) met the CBF criteria for post-CAS HPP on the SPECT imaging performed the next day. Of these patients, one developed cerebral HPS with symptoms of headache and confusion, which were resolved without neurological deficits by strict control of blood pressure (<80 mmHg) under coma therapy. The results of the univariate analysis of factors related to the development of cerebral HPP after CAS are summarized in Table 1. Female sex, degree of stenosis, and contralateral stenosis were significantly associated with the development of post-CAS cerebral hyperperfusion ($p<0.05$).

The preoperative cerebral perfusion analyses using SEE method are shown in Table 2. CBF at rest was not associated with HPP in the ACA, MCA, and PCA areas. CBF after acetazolamide, asymmetry index at rest, and CVR were significantly associated with HPP after CAS in the ACA, MCA, and PCA areas ($p<0.05$).

The cerebral perfusion analyses using ROI method are shown in Table 3. CBF at rest was not associated with HPP in all areas. As with the SEE method, CBF after acetazolamide, asymmetry index, and CVR were significantly associated with HPP after CAS in all areas ($p<0.05$).

The highest value of the AUC (0.981) of CVR was marked in the MCA area by the SEE method (Table 2). The CVR of the MCA area in patients with and without HPP was -15.9 ± 14.0 and 23.5 ± 17.1, respectively ($p<0.001$). In addition, the highest value of the AUC (0.868) of asymmetry index at rest was marked in the posterior part of the MCA area by the

ROI method (Table 3). The asymmetry index of this area in patients with and without HPP was 0.83 ± 0.08 and 0.97 ± 0.09, respectively ($p<0.001$). Among all perfusion data measured by both the SEE and ROI methods, the CVR in the MCA area by SEE method had the highest value of AUC.

When the three factors (female sex, contralateral stenosis, and degree of ipsilateral stenosis) that showed a significant difference by univariate analyses and CVR of the MCA area by SEE method were included as confounders in the logistic regression model for the multivariate analysis, only CVR of the MCA area by SEE method (OR, 0.720; CIs, 0.526-0.987) was significantly associated with the development of postoperative cerebral hyperperfusion ($p=0.041$, Table 4). The ROC curve of the CVR showed a cutoff value of -0.60% for the prediction of HPP, with a sensitivity of 0.946 and specificity of 1.000 ($p<0.001$, Figure 2).

Discussion

The present study found that the preoperative mean CVR of the whole MCA area measured on SEE analysis, which theoretically produces consistent results across examiners and institutions, had a significant predictive value for HPP after CAS. Using a cutoff value of -0.60% for CVR, the sensitivity and specificity were 94.6% and 100%, respectively, demonstrating that CVR was a good predictive factor. The predictive capability of CVR to

acetazolamide was better than the asymmetry index at rest, consistent with a previous study on the predictive factors of cerebral hyperperfusion after CEA [14]. The factor, which had the highest AUC by asymmetry index at rest, was the posterior part of the MCA by the ROI method (0.868 of the AUC). The ROC curve analysis of asymmetry index in posterior part of the MCA showed a cutoff value of 0.86 for the prediction of HPP, with a sensitivity of 0.932 and specificity of 0.800 ($p<0.001$, data not shown). Although the asymmetry index is a relatively good predictor of HPP following CAS, false negatives (developing HPP contrary to expectation) exist, which is different from CVR. Complications of endovascular treatment may be associated with disastrous consequences, thus false negatives should be avoided [25, 26]. Because acetazolamide is associated with frequent adverse effects, including metabolic acidosis, hypokalemia, numbness of the extremities, headache, tinnitus, gastrointestinal disturbances, and Stevens-Johnson syndrome, the asymmetry index at rest, which is evaluated without administration of acetazolamide, may be useful to screen for the need for acetazolamide administration [27, 28].

The pathophysiological mechanism of cerebral HPS remains unclear. Traditionally, HPS is attributed to the failure of normal cerebral autoregulation, secondary to long-standing changes in perfusion pressure. Maximal dilation of cerebral arterioles for long periods of time causes a loss of CBF autoregulation in areas of chronically under-perfused brain tissue and can result in hemorrhage and/or edema [6, 4, 14, 8]. In the present study, all patients with

HPP had a preoperative CVR <0%, which means that the CBF decreased after acetazolamide administration. Although the particular mechanism of this “steal phenomenon” by acetazolamide has not been clarified, it is thought to occur in the territory with the maximum vasodilatation of the cerebral vascular bed under chronic hemodynamic stress, which could explain the association between postoperative cerebral hyperperfusion and the preoperative steal phenomenon by acetazolamide [29, 30]. Chronic hypoperfusion due to carotid artery stenosis is believed to induce cerebral infarction, and one previous report showed that symptomatic patients tend to experience HPP after CEA [14]. To our knowledge, there is no report (including the present study) demonstrating a significant relationship between symptomatic stenosis and HPP after CAS [3].

The SEE method analyzes the whole MCA territory, and therefore we excluded patients who had a relatively large old infarction in the MCA area [15]. CVRs of the ACA and PCA are less predictable than that of the MCA for HPP after CAS. CBF in the ACA and PCA territories can be highly influenced by collateral flow from the anterior and posterior communicating arteries. Additionally, the CVR of the MCA area reflects all factors, including main flow from the MCA and collateral flow from the ACA and PCA areas. These characteristics of the MCA area are considered to be the reason for higher predictable value of HPP than the ACA and PCA areas. Low CVR by the SEE method indicates widespread hypoperfusion in the whole range of the MCA area, whereas hypoperfusion by the ROI

method reflects hypoperfusion within the localized area, which is considered to explain the predictable capability of the SEE method.

The development of HPP is reported to occur in 6.8-18.5% of patients after CAS, and the 11.9% incidence of HPP observed in this study is comparable to the reported incidences [2-4, 18]. HPS can occur in a proportion of patients with HPP, and the reported incidence of HPS is 0.7–6.8% after CAS [8, 1, 31, 6, 9]. Although several reports defined HPP as increasing ipsilateral CBF over 100% from baseline (200% compared with preoperative baseline)[6, 13, 32, 33], moderate relative hyperperfusion of the ipsilateral hemisphere was also reported to bring about HPS [34]. In the present study, we defined HPP as a resting CBF of >120% in the affected hemisphere compared with the unaffected side [18]. The diagnosis of HPP development with SPECT in this study was performed the day after CAS, based on the evidence that cerebral hyperperfusion after CAS most often occurred within 12 hours of the procedure [8, 6, 31, 1].

Contralateral (bilateral) carotid artery stenosis was reported to be a risk factor for cerebral hyperperfusion[1], and in the present study, univariate logistic analysis showed that contralateral stenosis was a significant risk factor for cerebral HPP following CAS. In the present study, the preoperative resting CBF in the contralateral MCA area with and without contralateral carotid artery stenosis was 34.2 ± 5.1 and 37.2 ± 7.9 ml/100 g/min, respectively. Although there was no significant difference in CBF in the contralateral MCA area ($p=0.074$),

a slightly decreased CBF in the contralateral MCA area provokes impairment of ipsilateral cerebral perfusion due to poor collateral flow, which contributes to the development of cerebral hyperperfusion following CAS.

Regarding demographic factors, 5/10 patients who developed HPP after CAS were female, and female sex was a significant predictor of HPP development by univariate analysis in the present study. Coutts et al. and Morrish et al. demonstrated that 2/3 and 2/4 patients with postoperative HPS after CAS were female,[8, 9] and another report demonstrated that female sex was associated with a decreased CVR [35]. Although these reports suggest female patients are at a higher risk for cerebral hyperperfusion following CAS, to the best of our knowledge, there is no remarkable evidence of a higher risk for female patients for developing postoperative cerebral hyperperfusion.

The most important perioperative management strategies for the prevention of HPS are controlling systemic blood pressure and the subsequent rise in cerebral perfusion [1, 8]. Additional strategies to avoid cerebral hyperperfusion include staged angioplasty, which is conventional angioplasty in the first session followed by CAS in the second session [18, 23]. In our series, one patient who underwent staged angioplasty did not develop HPP after CAS, and this case was not included in the analyses. Other reported stepwise revascularizations were superficial temporal artery-MCA anastomosis followed by CEA and angioplasty followed by CEA, and there was no evidence that these methods prevented cerebral

hyperperfusion [36, 37].

Various cerebral perfusion tracers, including ^{123}I-IMP, ^{99m}Tc-hexam-ethyl-propyleneamine oxime (HMPAO), and ^{99m}Tc-ethyl-cys-teinate dimer (ECD), have been used in the measurement of CBF by SPECT. These tracers necessitate underestimation of CBF in the high flow regions due to the nonlinear relationship between CBF and brain uptake of these tracers [38]. Among these tracers, IMP was reported to have a closer linear relationship than HMPAO and ECD; thus, we selected IMP for measurement of CBF [38,39].

This study has some limitations. First, it was a retrospective analysis with a small sample size. The number of female patients in this study was low (11/84); although, female sex was a significant factor of HPP by univariate logistic analysis. Second, this study evaluated the occurrence of HPP, and the results cannot be applied to the occurrence of symptomatic HPP (HPS) or intracranial hemorrhage following CAS. Finally, the ROI method was evaluated in only a single slice, and our study does not include analysis of the basal ganglia.

Conclusion

SPECT using the SEE method can analyze brain perfusion data objectively and reproducibly, in contrast with the ROI method. Logistic regression analysis demonstrated that reduced preoperative CVR was significantly associated with the development of cerebral HPP following CAS. The present study shows that the objective evaluation of cerebral

hemodynamic impairment using the SEE analysis could identify patients at risk for hyperperfusion after CAS.

References

[1] Abou-Chebl A, Yadav JS, Reginelli JP et al. Intracranial hemorrhage and hyperperfusion syndrome following carotid artery stenting: risk factors, prevention, and treatment. J Am Coll Cardiol 2004;43:1596-601.

[2] Iwata T, Mori T, Miyazaki Y et al. Global oxygen extraction fraction by blood sampling to anticipate cerebral hyperperfusion phenomenon after carotid artery stenting. Neurosurgery 2014;75:546-51; discussion 51.

[3] Iwata T, Mori T, Tajiri H et al. Predictors of hyperperfusion syndrome before and immediately after carotid artery stenting in single-photon emission computed tomography and transcranial color-coded real-time sonography studies. Neurosurgery 2011;68:649-55; discussion 55-6.

[4] Kaku Y, Yoshimura S, Kokuzawa J. Factors predictive of cerebral hyperperfusion after carotid angioplasty and stent placement. AJNR Am J Neuroradiol 2004;25:1403-8.

[5] Miyachi S, Taki W, Sakai N et al. Historical perspective of carotid artery stenting in Japan: analysis of 8,092 cases in The Japanese CAS survey. Acta Neurochir (Wien) 2012;154:2127-37.

[6] Ogasawara K, Sakai N, Kuroiwa T et al. Intracranial hemorrhage associated with cerebral hyperperfusion syndrome following carotid endarterectomy and carotid artery stenting: retrospective review of 4494 patients. J Neurosurg 2007;107:1130-6.

[7] McCabe DJ, Brown MM, Clifton A. Fatal cerebral reperfusion hemorrhage after carotid stenting. Stroke 1999;30:2483-6.

[8] Coutts SB, Hill MD, Hu WY. Hyperperfusion syndrome: toward a stricter definition. Neurosurgery 2003;53:1053-58; discussion 8-60.

[9] Morrish W, Grahovac S, Douen A et al. Intracranial hemorrhage after stenting and angioplasty of extracranial carotid stenosis. AJNR Am J Neuroradiol 2000;21:1911-6.

[10] van Mook WN, Rennenberg RJ, Schurink GW et al. Cerebral hyperperfusion syndrome. Lancet Neurol 2005;4:877-88.

[11] Uchiyama N, Misaki K, Mohri M et al. Association between carotid plaque composition assessed by multidetector computed tomography and cerebral embolism after carotid stenting. Neuroradiology 2012;54:487-93.

[12] Misaki K, Uchiyama N, Mohri M et al. Prediction of carotid artery in-stent restenosis by quantitative assessment of vulnerable plaque using computed tomography. J Neuroradiol 2016;43:18-24.

[13] Hosoda K, Kawaguchi T, Ishii K et al. Prediction of hyperperfusion after carotid endarterectomy by brain SPECT analysis with semiquantitative statistical mapping method. Stroke 2003;34:1187-93.

[14] Oshida S, Ogasawara K, Saura H et al. Does preoperative measurement of cerebral blood

flow with acetazolamide challenge in addition to preoperative measurement of cerebral blood flow at the resting state increase the predictive accuracy of development of cerebral hyperperfusion after carotid endarterectomy? Results from 500 cases with brain perfusion single-photon emission computed tomography study. Neurol Med Chir (Tokyo) 2015;55:141-8.
[15] Suga Y, Ogasawara K, Saito H et al. Preoperative cerebral hemodynamic impairment and reactive oxygen species produced during carotid endarterectomy correlate with development of postoperative cerebral hyperperfusion. Stroke 2007;38:2712-7.
[16] Tomura N, Otani T, Koga M et al. Correlation between severity of carotid stenosis and vascular reserve measured by acetazolamide brain perfusion single photon emission computed tomography. J Stroke Cerebrovasc Dis 2013;22:166-70.
[17] Mizumura S, Nakagawara J, Takahashi M et al. Three-dimensional display in staging hemodynamic brain ischemia for JET study: objective evaluation using SEE analysis and 3D-SSP display. Ann Nucl Med 2004;18:13-21.
[18] Yoshimura S, Kitajima H, Enomoto Y et al. Staged angioplasty for carotid artery stenosis to prevent postoperative hyperperfusion. Neurosurgery 2009;64:ons122-8; discussion ons8-9.
[19] Iida H, Itoh H, Nakazawa M et al. Quantitative mapping of regional cerebral blood flow using iodine-123-IMP and SPECT. J Nucl Med 1994;35:2019-30.
[20] Nishizawa S, Iida H, Tsuchida T et al. Validation of the dual-table autoradiographic method to quantify two sequential rCBFs in a single SPET session with N-isopropyl-[123I] p-iodoamphetamine. Eur J Nucl Med Mol Imaging 2003;30:943-50.
[21] Wodarz R. Watershed infarctions and computed tomography. A topographical study in cases with stenosis or occlusion of the carotid artery. Neuroradiology 1980;19:245-8.
[22] Ogasawara K, Inoue T, Kobayashi M et al. Pretreatment with the free radical scavenger edaravone prevents cerebral hyperperfusion after carotid endarterectomy. Neurosurgery 2004;55:1060-6.
[23] Uchida K, Yoshimura S, Shirakawa M et al. Experience of Staged Angioplasty to Avoid Hyperperfusion Syndrome for Carotid Artery Stenosis. Neurol Med Chir (Tokyo) 2015;55:824-9.
[24] North American Symptomatic Carotid Endarterectomy Trial. Methods, patient characteristics, and progress. Stroke 1991;22:711-20.
[25] Misaki K, Uchiyama N, Mohri M et al. Pseudoaneurysm formation caused by the withdrawal of a Trevo ProVue stent at a tortuous cerebral vessel: a case report. Acta Neurochir (Wien) 2016;158:2085-8.
[26] Misaki K, Uchiyama N, Nambu I et al. Optimizing the Volume of the Initial Framing Coil to Facilitate Tight Packing of Intracranial Aneurysms. World Neurosurg 2016;90:397-402.
[27] Ogasawara K, Tomitsuka N, Kobayashi M et al. Stevens-Johnson syndrome associated with intravenous acetazolamide administration for evaluation of cerebrovascular reactivity. Case report. Neurol Med Chir (Tokyo) 2006;46:161-3.
[28] Saito H, Ogasawara K, Suzuki T et al. Adverse effects of intravenous acetazolamide

administration for evaluation of cerebrovascular reactivity using brain perfusion single-photon emission computed tomography in patients with major cerebral artery steno-occlusive diseases. Neurol Med Chir (Tokyo) 2011;51:479-83.
[29] Kuwabara Y, Ichiya Y, Sasaki M et al. Time dependency of the acetazolamide effect on cerebral hemodynamics in patients with chronic occlusive cerebral arteries. Early steal phenomenon demonstrated by [150]H2O positron emission tomography. Stroke 1995;26:1825-9.
[30] Nariai T, Senda M, Ishii K et al. Posthyperventilatory steal response in chronic cerebral hemodynamic stress: a positron emission tomography study. Stroke 1998;29:1281-92.
[31] Meyers PM, Higashida RT, Phatouros CC et al. Cerebral hyperperfusion syndrome after percutaneous transluminal stenting of the craniocervical arteries. Neurosurgery 2000;47:335-43; discussion 43-5.
[32] Sundt TM, Jr., Sharbrough FW, Piepgras DG et al. Correlation of cerebral blood flow and electroencephalographic changes during carotid endarterectomy: with results of surgery and hemodynamics of cerebral ischemia. Mayo Clin Proc 1981;56:533-43.
[33] Piepgras DG, Morgan MK, Sundt TM, Jr. et al. Intracerebral hemorrhage after carotid endarterectomy. J Neurosurg 1988;68:532-6.
[34] Karapanayiotides T, Meuli R, Devuyst G et al. Postcarotid endarterectomy hyperperfusion or reperfusion syndrome. Stroke 2005;36:21-6.
[35] Chaer RA, Shen J, Rao A et al. Cerebral reserve is decreased in elderly patients with carotid stenosis. J Vasc Surg 2010;52:569-74; discussion 74-5.
[36] Egashira Y, Yoshimura S, Yamada K et al. Stepwise revascularization by carotid endarterectomy after balloon angioplasty for symptomatic severe carotid artery stenosis. Ann Vasc Surg 2012;26:731 e9-13.
[37] Yoshimoto T, Shirasaka T, Yoshidumi T et al. Stepwise revascularization for prevention of postoperative hyperperfusion. Neurol Med Chir (Tokyo) 2006;46:283-7; discussion 8-9.
[38] Tsuchida T, Yonekura Y, Nishizawa S et al. Nonlinearity correction of brain perfusion SPECT based on permeability-surface area product model. J Nucl Med 1996;37:1237-41.
[39] Ohnishi T, Yano T, Nakano S et al. Acetazolamide challenge and technetium-99m-ECD versus iodine-123-IMP SPECT in chronic occlusive cerebrovascular disease. J Nucl Med 1997;38:1463-7.

Figure legends

Figure 1

A: Representative case with the development of cerebral hyperperfusion. Preoperative cerebral blood flow (CBF) at rest (left) and after the administration of acetazolamide (ACZ; middle) showed a marked decrease in CBF in the left middle cerebral artery (MCA) area after ACZ. Asymptomatic cerebral hyperperfusion occurred the day after carotid artery stenting (right).

B: The stereotactic extraction estimation (SEE) method demonstrated CBF of the anterior cerebral artery (ACA), MCA, and posterior cerebral artery (PCA) at rest and after acetazolamide. The SEE analyses also automatically calculated the cerebrovascular reactivity (CVR) of each region. The border zone of ACA, MCA, and PCA, which was automatically set by these analyses, is shown on the brain surface image (arrows).

C: Perfusion analyses using the region of interest (ROI) method of a representative case is shown. The ACA, anterior and posterior part of the MCA, anterior and posterior part of white matter (WM), and PCA were placed on the slice at the anterior commissure-posterior commissure level +20 mm. CBF at rest and after ACZ, asymmetry index (AI), and CVR of each region is presented.

Figure 2

Receiver-operating characteristic curve of the cerebrovascular reactivity (CVR) of the middle cerebral artery area using the stereotactic extraction estimation (SEE) method for prediction of the cerebral hyperperfusion phenomenon (HPP) after carotid artery stenting. The area under the curve was 0.981, and a cutoff value of -0.60% for the prediction of HPP with a sensitivity of 0.946 and specificity of 1.000 ($p<0.001$)

Table 1. Univariate analysis of clinical characteristics related to the development of cerebral hyperperfusion after carotid artery stenting

Variables	Cerebral Hyperperfusion		*P* Value
	Yes (n = 10)	No (n = 74)	
Age, y	73.1±6.3	69.8±7.2	0.109
Female	5 (50%)	6 (8%)	0.003
Symptomatic lesion	8 (80%)	51 (69%)	0.716
Degree of stenosis, %	86.1±9.4	72.7±18.1	0.026
Contralateral stenosis	5 (50%)	11 (15%)	0.019
Risk factors			
Hypertension	10 (100%)	51 (69%)	0.055
Diabetes mellitus	3 (30%)	35 (48%)	0.500
Dyslipidemia	5 (50%)	30 (41%)	0.735
Renal insufficiency	3 (30%)	23 (31%)	1.000
Current smoking	2 (20%)	17 (23%)	1.000
Medication			
Aspirin	10 (100%)	74 (100%)	1.000
Clopidogrel	10 (100%)	69 (93%)	0.698
Cilostazol	3 (30%)	22 (30%)	1.000
Statin	9 (90%)	52 (71%)	0.272
CAS procedure			
Balloon protection	2 (20%)	15 (21%)	1.000
Predilatation	10 (100%)	67 (91%)	0.591
Open-cell stent	5 (50%)	35 (47%)	1.000
Postdilatation	7 (70%)	63 (85%)	0.359

Peak systolic velocity, cm/s			
Pre-CAS	392±252	424±181	0.475
Post-CAS	139±92	113±47	0.239

CAS: carotid artery stenting

Table 2. Univariate analysis of cerebral perfusion analyses using the stereotactic extraction estimation method related to the development of cerebral hyperperfusion after carotid artery stenting

Cerebral perfusion data		Cerebral Hyperperfusion		AUC	95% confidence interval	*P* Value
		Yes (n = 10)	No (n = 74)			
ACA	CBF at rest, ml/100 g/min	33.3 ± 4.2	35.9 ± 7.5	0.607	0.446 - 0.768	0.275
	CBF after ACZ, ml/100 g/min	30.9 ± 5.5	44.1 ± 10.7	0.901	0.823 - 0.979	<0.001
	Asymmetry index at rest	0.93 ± 0.08	0.98 ± 0.05	0.703	0.496 - 0.910	0.038
	CVR, %	-7.1 ± 12.8	22.7 ± 14.3	0.970	0.937 - 1.000	<0.001
MCA	CBF at rest, ml/100g/min	32.0 ± 4.3	35.0 ± 7.2	0.641	0.484 - 0.798	0.149
	CBF after ACZ, ml/100 g/min	26.9 ± 6.0	43.1 ± 9.7	0.926	0.862- 0.989	<0.001
	Asymmetry index at rest	0.85 ± 0.09	0.97 ± 0.09	0.804	0.658 - 0.950	0.002
	CVR, %	-15.9 ± 14.0	23.5 ± 17.1	0.981	0.956 - 1.000	<0.001
PCA	CBF at rest, ml/100 g/min	36.2 ± 6.8	37.4 ± 7.0	0.572	0.393 - 0.751	0.460
	CBF after ACZ, ml/100 g/min	41.0 ± 13.9	50.0 ± 9.8	0.734	0.532 - 0.935	0.017
	Asymmetry index at rest	0.91 ± 0.07	0.98 ± 0.05	0.800	0.665 - 0.935	0.002
	CVR, %	13.2 ± 29.7	33.7 ± 15.2	0.714	0.498 - 0.929	0.029

ACZ: acetazolamide, AUC: area under the curve, CAS: carotid artery stenting, CBF: cerebral blood flow, CVR: cerebrovascular reactivity, SEE: stereotactic extraction estimation

Table 3. Univariate analysis of cerebral perfusion analyses using the region of interest method related to the development of cerebral hyperperfusion after carotid artery stenting

Cerebral blood flow		Cerebral Hyperperfusion		AUC	95% confidence interval	*P* Value
		Yes (n = 10)	No (n = 74)			
ACA	CBF at rest, ml/100 g/min	29.1 ± 4.4	32.2 ± 8.5	0.618	0.460 - 0.775	0.229
	CBF after ACZ,ml/100 g/min	26.4 ± 6.6	40.5 ±12.4	0.870	0.775 - 0.966	<0.001
	Asymmetry index at rest	0.90 ± 0.13	0.99 ±0.13	0.746	0.589 - 0.903	0.012
	CVR, %	-9.3 ± 15.7	26.3 ±21.8	0.926	0.861 - 0.990	<0.001
MCA anterior	CBF at rest, ml/100 g/min	30.2 ± 4.1	33.5 ± 8.3	0.635	0.480 - 0.790	0.167
	CBF after ACZ,ml/100 g/min	24.6 ± 5.2	41.7 ±12.7	0.923	0.863 - 0.983	<0.001
	Asymmetry index at rest	0.87 ± 0.16	0.98 ±0.28	0.655	0.437 - 0.874	0.112
	CVR, %	-18.4 ±12.7	24.5 ±21.5	0.973	0.941 - 1.000	<0.001
MCA posterior	CBF at rest, ml/100 g/min	31.8 ± 6.1	34.9 ± 8.1	0.647	0.472 - 0.821	0.134
	CBF after ACZ,ml/100 g/min	24.9 ± 6.4	43.3 ±13.5	0.923	0.852 - 0.994	<0.001
	Asymmetry index at rest	0.83 ± 0.08	0.97 ±0.09	0.868	0.723 - 1.000	<0.001
	CVR, %	-21.6 ±14.7	23.7 ±21.5	0.969	0.934 - 1.000	<0.001
PCA	CBF at rest, ml/100 g/min	37.6 ± 7.6	38.4 ± 8.9	0.528	0.346 - 0.711	0.772
	CBF after ACZ,ml/100 g/min	40.7 ± 16.9	50.6 ±12.6	0.743	0.554 - 0.933	0.013
	Asymmetry index at rest	0.87 ± 0.08	0.97 ±0.10	0.776	0.652 - 0.900	0.005
	CVR, %	7.4 ± 30.6	32.7 ±19.5	0.757	0.585 - 0.929	0.009
WM anterior	CBF at rest, ml/100 g/min	30.6 ± 3.7	33.4 ± 9.0	0.564	0.411 - 0.718	0.512
	CBF after ACZ,ml/100 g/min	22.8 ± 4.8	39.6 ±12.1	0.935	0.881 - 0.989	<0.001
	Asymmetry index at rest	0.84 ± 0.11	0.97 ±0.16	0.797	0.659 - 0.935	0.002
	CVR, %	-25.3 ±13.3	18.8 ±21.7	0.961	0.920 - 1.000	<0.001
WM posterior	CBF at rest, ml/100 g/min	32.1 ± 4.6	34.6 ± 8.4	0.599	0.435 - 0.764	0.310
	CBF after ACZ,ml/100 g/min	21.8 ± 6.6	39.3 ±11.8	0.916	0.842 - 0.990	<0.001
	Asymmetry index at rest	0.86 ± 0.11	0.98 ±0.10	0.846	0.675 - 1.000	<0.001
	CVR, %	-32.5 ±17.0	13.6 ±20.9	0.955	0.913 - 0.998	<0.001

ACZ: acetazolamide, AUC: area under the curve, CAS: carotid artery stenting, CBF: cerebral blood flow, CVR: cerebrovascular reactivity, ROI: region of interest, WM: white matter

Table 4. Multivariate logistic regression analysis results

	Odds ratio (95% confidence interval)	*P* value
Female	829.973 (0.502 – 1371393.865)	NS
Contralateral stenosis	134.642 (0.435 – 41647.018)	NS
Degree of stenosis	0.917 (0.740 – 1.136)	NS
CVR	0.720 (0.526 – 0.987)	0.041

CVR: cerebrovascular reactivity

Figure 1

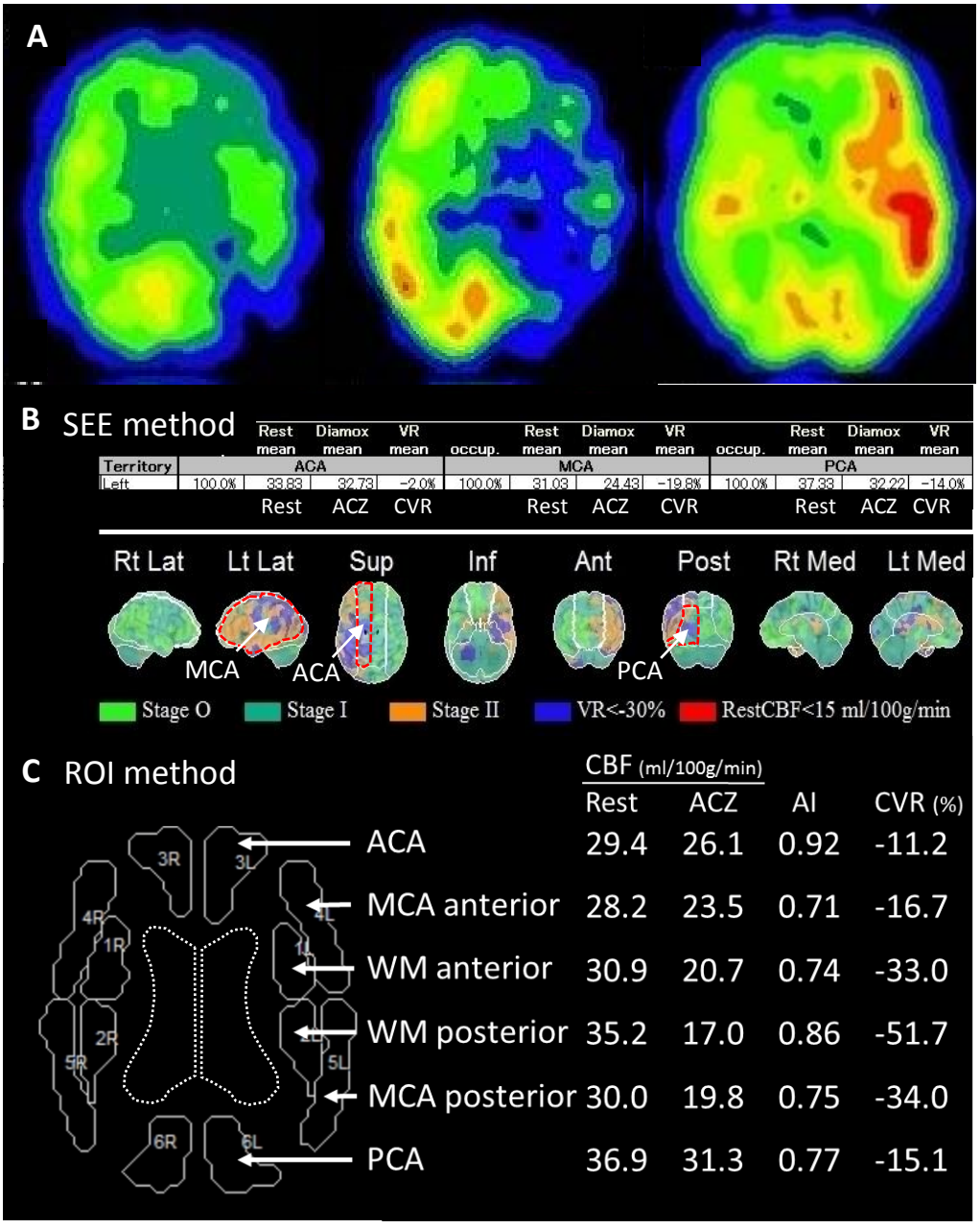
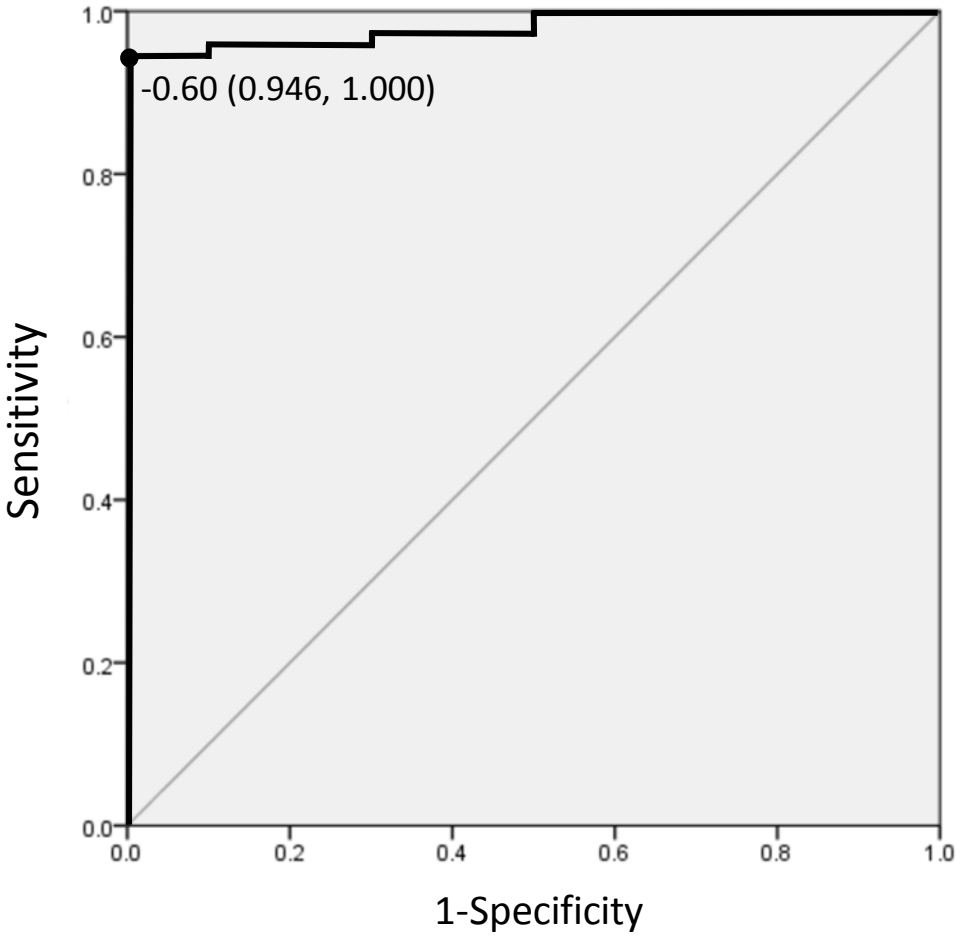

A
B SEE method
Territory
ACA
MCA
PCA
Left
100.0% 33.83 32.73 -2.0% 100.0% 31.03 24.43 -19.8% 100.0% 37.33 32.22 -14.0%
Rest ACZ CVR
Rt Lat
Lt Lat
Sup
Inf
Ant
Post
Rt Med
Lt Med
MCA
ACA
PCA
Stage O
Stage I
Stage II
VR<-30%
RestCBF<15 ml/100g/min
C ROI method
CBF (ml/100g/min)
Rest ACZ AI CVR (%)
ACA 29.4 26.1 0.92 -11.2
MCA anterior 28.2 23.5 0.71 -16.7
WM anterior 30.9 20.7 0.74 -33.0
WM posterior 35.2 17.0 0.86 -51.7
MCA posterior 30.0 19.8 0.75 -34.0
PCA 36.9 31.3 0.77 -15.1
3R
3L
4R
4L
1R
1L
2R
2L
5R
5L
6R
6L

Figure 2


1.0
0.8
0.6
0.4
0.2
0.0
Sensitivity
-0.60 (0.946, 1.000)
0.0
0.2
0.4
0.6
0.8
1.0
1-Specificity