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Prediction of Hyperperfusion After Carotid Endarterectomy by Brain SPECT Analysis With Semiquantitative Statistical Mapping Method

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- **Background and Purpose**—Hyperperfusion syndrome is a rare but disastrous complication after carotid endarterectomy (CEA). The aim of this study was to investigate the relationship between preoperative cerebral blood flow (CBF) abnormalities and postoperative hyperperfusion through the use of statistical brain mapping analysis.
- *Methods*—For 41 patients with unilateral carotid stenosis ≥70%, CBF and cerebral vasoreactivity (CVR) were investigated with resting and acetazolamide-challenge single photon emission CT before CEA. CBF 1 day after CEA was also measured. Three-dimensional stereotactic surface projection (3D-SSP) analysis of CBF changes was performed by use of a control database of 20 subjects.
- **Results**—Patients with reduced CVR (CVR <10%, n=15) were categorized into 2 groups based on the severity of CBF reduction relative to the control database by 3D-SSP analysis without normalization: type I (ipsilateral CBF decrease <20%, n=8) and type II (ipsilateral CBF decrease \geq 20%, n=7). With thalamic normalization, the patients were also categorized into 2 groups: type A (ipsilateral *Z* score \leq 2, n=10) and type B (ipsilateral *Z* score >2, n=5). Severe CBF reduction (\geq 20% or *Z* score >2) was significantly associated with postoperative hyperperfusion (CBF increase \geq 100%). However, 3D-SSP with thalamic normalization (*Z* score) demonstrated a higher predictive value (80%) and specificity (91%) for hyperperfusion than 3D-SSP without normalization (percent reduction) (57% and 73%, respectively). No patients with normal CVR (CVR \geq 10%, n=26) demonstrated postoperative hyperperfusion.
- *Conclusions*—Objective evaluation of abnormalities of CBF and CVR with 3D-SSP could identify patients at risk for postoperative hyperperfusion. (*Stroke*. 2003;34:1187-1193.)

Key Words: brain ■ carotid endarterectomy ■ carotid stenosis ■ tomography, emission-computed, single-photon

yperperfusion syndrome is a rare but disastrous compli-Cation after carotid endarterectomy (CEA). Among the classic triad of unilateral headache, seizures, and intracerebral hemorrhage,1-3 intracerebral hemorrhage is reported to occur in 0.4% to 2.1% of patients after CEA.^{1,3-6} The prognosis is miserable, with mortality rates of 36% to 63%, and survivors have significant morbidity. Risk factors of this syndrome include hypertension, high-grade stenosis, poor collateral flow, and contralateral carotid occlusion.7 Recently, we reported that severely impaired cerebral vasoreactivity (CVR) detected by single photon emission CT (SPECT) is significantly associated with postoperative hyperperfusion.8 In addition, severe and diffuse asymmetric pattern of preoperative cerebral blood flow (CBF) reduction seemed to be characteristic of patients who experienced postoperative hyperperfusion.8 However, the relationship between preoperative CBF reduction and postoperative hyperperfusion has not been fully clarified.

Most CBF studies used region of interest (ROI) approaches. These techniques have several disadvantages. The analysis does not include the entire brain; the density of the data sampling can be biased regionally; and reproducibility and consistency among different investigators are limited because of difference in experience of observers.⁹ To overcome these issues, advances in image processing have been developed for positron emission tomography (PET) and SPECT in a 3-dimensional data extraction format.^{9–11} Three-dimensional stereotactic surface projection (3D-SSP) is a fully automated, user-independent data extraction method that has been applied extensively to PET image analysis in Alzheimer's disease¹⁰ and other neurological disorders.

The present study used statistical brain mapping techniques for SPECT imaging to investigate CBF and CVR in carotid stenosis. We investigated whether this new technique could demonstrate a significant relationship between preoperative CBF abnormalities and hyperperfusion after CEA.

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Subjects and Methods

Between March 1999 and April 2002, 77 consecutive patients underwent CEA with in-dwelling shunt in Hyogo Brain and Heart Center, 41 of whom fulfilled the following criteria and entered the present study. Inclusion criterion was unilateral internal carotid artery (ICA) stenosis \geq 70%. Exclusion criteria were contralateral carotid stenosis \geq 30%, intracranial artery stenosis or occlusion, and/or major disabling stroke.

Of the 41 patients, 35 were male and 6 were female. Mean age was 69.8 ± 7.5 years (mean \pm SD; range, 49 to 84 years). Thirty-three patients were hypertensive, and 13 had diabetes mellitus. Transient ischemic attacks referring to the relevant ICA were the only symptoms for 8 patients. Four patients had suffered transient ischemic attacks with subsequent strokes, and 13 patients had suffered strokes only. All stroke patients had made good functional recoveries. Sixteen patients exhibited asymptomatic ICA stenosis.

Preoperative CT and MRI demonstrated ipsilateral symptomatic infarctions in 19 patients, ipsilateral asymptomatic infarctions in 3, and contralateral asymptomatic infarction in 2. Two patients had old infarction in the pons and/or cerebellum. No infarction was seen in 19 patients.

The overall average of the degree of ICA stenosis was $83.5\pm11.3\%$ (range, 70% to 99%) on angiography.¹² Twenty patients underwent surgery on the left side and 21 on the right side under general anesthesia. We obtained informed consent from all patients or their next of kin.

CBF Studies

Resting CBF was assessed by SPECT with a rotating dual-headed gamma camera (GAMA View SPECT 2000 H-20, Hitachi) before and 1 day after CEA. Details of the procedure with *N*-isopropyl-p-[¹²³I]-iodoamphetamine (IMP) using arterial blood sampling and a microsphere model^{13–15} were described previously.⁸ In brief, 111 MBq (3 mCi) of ¹²³I-IMP was injected intravenously. Fifteen minutes later, SPECT acquisition was started. Five to 7 days after resting SPECT, 1 g acetazolamide was given intravenously; 20 minutes later, SPECT was repeated. The median time between the latest ipsilateral neurological event and preoperative SPECT study was 48 days (range, 18 to 168 days) for strokes and 47 days (range, 10 to 151 days) for transient ischemic attacks. The median time between the preoperative SPECT studies and CEA was 16 days (range, 6 to 73 days).

Image Analysis by ROI

We measured regional CBF (rCBF) by placing 6 to 10 ROIs (each 16×16 mm) in bilaterally symmetric regions of the middle cerebral artery territory on a SPECT image plane where the asymmetry was most prominent.⁸ The pairs that showed the largest difference in values were used. A region where infarction was seen on CT and/or MRI was carefully excluded from the evaluation.

The regional CVR (rCVR) was calculated as follows:

RCVR (%)=[(acetazolamide-challenge rCBF

-resting rCBF)×100]/resting rCBF.

Normal control values of rCBF and rCVR on ROI analysis were obtained.⁸ We had defined the values <12% as reduced CVR in the previous study.⁸ In the present study, however, we defined the values <10% as reduced CVR because it was more convenient and CVR values of all patients with CVR <12% were actually <10%. When CBF decreased after acetazolamide challenge, it was defined as intracerebral steal.¹⁶

Image Analysis by 3D-SSP

In brief, 3D-SSP involved 3 major steps.^{10,11,17} First, stereotactic anatomic standardization was performed. A rotational correction and a centering in 3 dimensions of the SPECT data set were performed,¹⁷ followed by realignment to the anterior commissure–posterior commissure line. The anterior commissure–posterior commissure line was estimated by iterative matching between the individual image

and a standard atlas template using mutual information.¹¹ Differences in size between the individual brain and standard template were removed by linear scaling. Thereafter, regional anatomic differences between the individual and atlas brain were minimized by an automated nonlinear warping.¹¹

In the second step, data extraction, $>16\,000$ surface pixels covering the lateral and medial surface of both hemispheres were predetermined in stereotactic coordinates. The peak cortical activity perpendicular to these pixels was projected onto the surface pixels. Thus, each brain was stereotactically transformed into a standard surface image format,¹⁰ which enabled us to compare the resultant cortical projections with a normal database.

The third step was comparison of the individual data with the normal control database. A normal control database for 3D-SSP was constructed by averaging image sets in 20 people (15 men, 5 women) who had no stenosis or occlusion of cervical or intracranial arteries. Mean age was 66.8 ± 8.5 years (range, 42 to 80 years). There was no statistically significant difference in age and sex between the control and patient groups.

At first, the absolute CBF value in each pixel was used for 3D-SSP analysis without pixel normalization. Reduction in absolute CBF values in each patient was compared with the normal control database of the absolute values, and the percent reduction of each pixel was displayed on 3D-SSP. Previous ROI study had demonstrated normal values of rCBF ($45.5\pm5.9 \text{ mL} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$),⁸ which means that 2 SD corresponds to 26% change. Therefore, we preliminarily compared 2 cutoff values (20% and 30%) of CBF reduction. The 20% CBF reduction was chosen because the 30% reduction was too insensitive to detect CBF reduction adequately. Accordingly, when pixels with a decrease of $\geq 20\%$ covered $\geq 50\%$ of areas of a hemisphere surface map, it was defined as decreased CBF on 3D-SSP. With this definition, we could nullify the influence of infarction on the evaluation of CBF because only small infarctions were seen in the present study. For 3D-SSP of CVR, CBF increase after acetazolamide challenge was expressed as percentages of corresponding values from resting CBF in each patient. For 3D-SSP of CBF increase after CEA, postoperative CBF increase was expressed as percentages of corresponding values from preoperative resting CBF. Hyperperfusion after CEA was defined CBF increase of \geq 100% on the first postoperative day, according to Piepgras et al.¹ When pixels with an increase of $\geq 100\%$ covered $\geq 25\%$ of areas of a hemisphere surface map, it was defined as hyperperfusion for 3D-SSP analysis. With this definition, only relatively widespread hyperperfusion could be recognized.

We also performed 3D-SSP analysis with normalization to reduce variances associated with absolute quantification. Pixel values of an individual's image set were normalized to the thalamic value before the analysis¹⁰ as follows: normalized CBF=(individual CBF)/(thalamic CBF).

The normalized activity of each patient was compared with the reference control database by means of a Z score. A Z score was calculated for each surface pixel: Z score=([normal mean]–[individual mean])/(normal SD). When pixels with a Z score >2 covered >50% of the areas of a hemisphere surface map, it was defined as a CBF decrease. We used a Z score of 2 as a cutoff value because it is commonly used to discriminate abnormalities. The probability of exceeding the threshold of Z score of 2 is $\approx 2\%$ (1 tail).

Statistical Analysis

Descriptive statistics are presented as mean \pm SD. For the comparison study, we used analysis of variance and Student's *t* test. Fisher's exact test was used for proportion analysis. Values of *P*<0.05 are reported to be significant. A commercially available software package was used (Statview 5.0, Abacus Concepts).

Results

ROI Analysis

The patients were categorized into 2 groups based on the preoperative status of CVR measured by the ROI ap-



Figure 1. Original SPECT transaxial slices of a patient with right ICA stenosis. Top, Preoperative resting SPECT. Severe hypoperfusion is seen in the right ICA territory. Middle, Preoperative acetazolamide (ACZ)-challenge SPECT. Very little CBF response to acetazolamide is seen in the same territory. Bottom, SPECT on the first postoperative day demonstrates hyperperfusion in the right ICA territory.

proach: normal CVR (rCVR $\geq 10\%$, n=26) or reduced CVR (rCVR <10\%, n=15). Ipsilateral CBF in the reduced CVR group (36.5±7.5 mL \cdot 100 g⁻¹ \cdot min⁻¹) was significantly lower than that in the control group (45.5±5.9 mL \cdot 100 g⁻¹ \cdot min⁻¹, n=10)⁸ (*P*=0.022), but ipsilateral CBF in the normal CVR group (41.7±8.3 mL \cdot 100 g⁻¹ \cdot min⁻¹) was not. In addition, all 4 patients who demonstrated postoperative hyperperfusion belonged to the reduced CVR group (Figure 1). Therefore, the analysis was

applied mainly to these 15 patients with reduced CVR.

Visualization of CBF and CVR by 3D-SSP

In the absolute value study, the extracted 3D-SSP data of resting CBF and acetazolamide-challenge CBF could be viewed from the right, left, superior, inferior, anterior, posterior, and 2 medial aspects of the brain (Figure 2, first and second rows). 3D-SSP also demonstrated surface maps of CVR on a pixel-by-pixel basis (Figure 2, third row). Visual-



Figure 2. 3D-SSP images of CBF SPECT data of the patient in Figure 1. Right lateral (R. LAT), left lateral (L. LAT), superior (SUP), inferior (INF), anterior (ANT), posterior (POST), right medial (R. MED), and left medial (L. MED) views. Rest indicates preoperative 3D-SSP of resting CBF. Severe hypoperfusion is seen in the right ICA territory. ACZ indicates preoperative 3D-SSP of acetazolamide-challenge SPECT. Very little CBF response to acetazolamide is seen in the same territory. CVR indicates 3D-SSP of CVR. Intracerebral steal is easily recognized as black pixels. CBF reduction indicates 3D-SSP of percent reduction in preoperative CBF. Post-CEA indicates 3D-SSP of CBF percent increase 1 day after CEA. Hyperperfusion is easily recognized as white pixels. Three rainbows display ranges of CBF for the first and second rows, CVR for the third row, CBF decrease for the fourth row, and CBF increase for the fifth row.



Figure 3. Relationship between pattern of preoperative CBF reduction and postoperative hyperperfusion. To make visual interpretation easier, the side of carotid stenosis is converted to the right in all patients. Left 3 columns, 3D-SSP of CBF percent decrease. Middle 3 columns, 3D-SSP of CVR. Right 3 columns, 3D-SSP of CBF percent increase 1 day after CEA. First row shows type I; second row, type II (symmetric type); third and fourth rows, type II (asymmetric type); and fifth row, type N. See text for details. Note that hyperperfusion occurred only in asymmetric type II. Three rainbows display ranges of CBF decrease and CVR and CBF increase.

ization of the CVR could be modified by changing a range of the color scale to make visual interpretation easier. For example, if a cutoff value is 0% as in Figure 2 (third row) and Figure 3 (middle 3 columns), a region of intracerebral steal is easily recognized as black pixels.

Relationship Between Preoperative CBF Decrease and Hyperperfusion After CEA

By 3D-SSP analysis of absolute value, patients in the reduced CVR group detected by the ROI method were further categorized into 2 groups based on the severity of the preoperative CBF decrease compared with the control database: type I (ipsilateral CBF decrease <20%, n=8) and type II (ipsilateral CBF decrease $\geq 20\%$, n=7) (Figure 3). In type II, some patients demonstrated symmetric CBF reduction (Figure 3, second row), and others demonstrated asymmetric CBF reduction (Figure 2, fourth row, and Figure 3, third and fourth rows). Type N (bilateral CBF decrease <20%) is a typical CBF pattern of patients in the normal CVR group (Figure 3, fifth row).

No patient exhibited postoperative intracerebral hemorrhage. In 4 patients, however, postoperative ipsilateral hyperperfusion (CBF increase $\geq 100\%$) was clearly observed on 3D-SSP of percent increase 1 day after CEA, although postoperative CT scans were normal. There was no significant difference in mean systolic blood pressure during SPECT measurement between patients with hyperperfusion (137±18 mm Hg, n=4) and those without hyperperfusion (131±16 mm Hg, n=11). Hyperperfusion was easily recognized as white pixels by setting the range of the color scale from 50% to 100% (Figure 2, fifth row, and Figure 3, right 3 columns). Incidence of hyperperfusion was significantly higher in type II (4 of 7, 57%) than in type I (0 of 8, 0%) (P=0.026) (the Table, middle). Sensitivity was 100%; specificity was 73%. All patients with hyperperfusion demonstrated an asymmetric pattern of CBF reduction. It is note-worthy that even patients with intracerebral steal did not experience postoperative hyperperfusion if the preoperative CBF reduction was <20% (Figure 3, first and second rows). On the contrary, there was no significant difference in incidence of hyperperfusion between type I (0 of 5, 0%) and type II (4 of 10, 40%) in ROI analysis on transaxial slices (the Table, top). Sensitivity was 100%, and specificity was 45%.

On 3D-SSP images with thalamic normalization, by setting a Z score of 2 as the cutoff value, an asymmetric pattern of

Relationship Between CBF Reduction and Hyperperfusion After CEA

		Hyperperfusion		Fichar's tost
Study Type	+	_	Incidence, %	(<i>P</i>)
ROI				
CBF decrease (percent reduction)				
<20%	0	5	0	NS
≥20%	4	6	40	(0.15)
30-SSP				
CBF decrease (percent reduction)				
Type I (<20%)	0	8	0	0.026
Type II (≥20%)	4	3	57	
CBF decrease (Z score)				
Type A (Z score \leq 2)	0	10	0	0.0037
Type B (Z score $>$ 2)	4	1	80	



Figure 4. Comparison between 3D-SSP with and without normalization. Side of carotid stenosis is converted to the right in all patients. Each case is the same as in Figure 3. Left, 3D-SSP of CBF percent reduction. Right, Corresponding 3D-SSP of statistical *Z* scores demonstrating areas of CBF reduction. A and B indicates type. See text for details. Note that the appearance of significant contralateral CBF reduction on 3D-SSP without normalization (left) disappeared by use of thalamic normalization (right). Left rainbow displays CBF decrease; right rainbow, *Z* score (1 to 5), although only areas with a *Z* score >2 are displayed on *Z* map.

CBF decrease was recognized more clearly than on 3D-SSP images of percent reduction without normalization (Figure 4). With the use of normalization, the appearance of significant contralateral CBF decrease disappeared. In all patients, the contralateral Z score was ≤ 2 . Therefore, the patients were categorized into 2 groups: type A (ipsilateral Z score ≤ 2 , n=10) and type B (ipsilateral Z score >2, n=5). Type A consisted of patients who belonged to types I and II with symmetric CBF reduction on 3D-SSP without normalization. Type B consisted of patients who belonged to type II with asymmetric CBF reduction on 3D-SSP without normalization. With normalization, the predictive value of CBF reduction for postoperative hyperperfusion was improved. Incidence of hyperperfusion was significantly higher in type B (4 of 5, 80%) than in type A (0 of 10, 0%) (P=0.0037) (the Table, bottom). Sensitivity was 100%; specificity was 91%. Even the final patient in type B demonstrated a CBF increase of $\geq 50\%$.

Discussion

In the present study, patterns of CBF abnormalities in carotid stenosis were investigated by 3D-SSP. This technique originally used normalization for data analysis.^{9,10} In addition to analysis with normalization, however, we used absolute values of CBF without normalization because it is essential to obtain the absolute values for calculation of CVR and postoperative CBF increase. The CVR to CO₂ or acetazol-amide has been proposed as a test for cerebral hemodynamic reserve.^{8,13,16,18} In these studies, vasoreactivity was evaluated by quantitative CBF measurement. Conventional qualitative

techniques are not appropriate for these kinds of analysis because they may incorrectly identify the ipsilateral cerebral hemodynamics as significantly compromised when the CBF increase after acetazolamide challenge is relatively higher in the contralateral than ipsilateral side.¹⁹

The template used in 3D-SSP analysis was developed specifically for the reference to the Talairach 1988 atlas.^{20,21} The template precisely represents the original shape because it was matched initially to the Talairach atlas through >400 identifiable landmarks. This will guarantee that the stereotactic coordinates in 3D-SSP analysis can be cross-referenced to the Talairach atlas for accurate signal localization. The current template was created by averaging a large number of normal [¹⁸F]fluorodeoxyglucose (FDG) PET data.²¹ The similarity between FDG and blood flow images permits the use of the FDG template for blood flow image analysis.

In the present study, strict statistical inference was not made on statistical maps because the purpose of this mapping analysis was to demonstrate the extent and pattern of regional CBF abnormalities. 3D-SSP clearly demonstrated percent decrease in CBF, impaired CVR, and postoperative percent increase in CBF on a pixel-by-pixel basis. By setting an appropriate cutoff value for display, 3D-SSP images allow simple recognition of these abnormalities, which is likely to increase the diagnostic accuracy. In addition, 3D-SSP was less affected by the atrophy that is often seen in the brain of patients with ischemic cerebrovascular disease.²² Furthermore, 3D-SSP is fully automated and does not require interference by the user. It seemed evident from these findings that abnormal cerebral circulation was more easily recognizable by this method compared with the conventional slice-based study. This is especially helpful when the reader is not experienced.

Hyperperfusion, which is defined as a CBF increase of \geq 100%, was reported to be a significant risk factor for intracerebral hemorrhage.^{1,6} Therefore, detection of hyperperfusion after CEA is important for prevention by starting strict control of blood pressure.^{3,6,7} Previous studies had suggested that patients with preoperative hemodynamic failure run a definite risk for hyperperfusion syndrome.^{1,3,8,23} In the present study, we again found that postoperative hyperperfusion was seen only in the reduced CVR group detected by ROI approach. However, it is noteworthy that even intracerebral steal did not necessarily result in hyperperfusion after CEA if the preoperative CBF reduction was not severe. It would be very convenient if a certain degree of baseline CBF reduction itself could identify patients at risk for hyperperfusion because it might enable omission of acetazolamide-challenge SPECT.

According to the pattern of preoperative percent reduction in CBF, we categorized the reduced CVR group into 2 subgroups: type I and type II. A significant CBF increase on the first postoperative day was seen only in type II but not in type I, and this difference was statistically significant on 3D-SSP analysis but not on ROI analysis. The 3D-SSP analysis demonstrated higher a predictive value and higher specificity for hyperperfusion than ROI analysis.

However, only 20% reduction in absolute CBF values is not enough to predict hyperperfusion because all patients with hyperperfusion demonstrated asymmetric pattern of CBF reduction. It is well known that there is a wide variation in global CBF across subjects. This variation could cause not only an appearance of ipsilateral CBF reduction but also an appearance of contralateral CBF reduction in some patients on 3D-SSP. Thus, normalization is very helpful in reducing global CBF variation. We used the thalamus as the reference region because it was reported to be the most robust reference region.9,10 In addition, some patients had old infarction in pons and/or cerebellum, which made these regions inappropriate as a reference region. However, CBF reduction in the thalamus was also apparent on the side of carotid stenosis in some patients. To circumvent this problem, the preserved side of the thalamus that had a higher value was used for normalization.

In fact, the asymmetric pattern of CBF reduction was recognized more clearly on 3D-SSP with normalization than without normalization. The significant contralateral CBF reduction vanished on the 3D-SSP with normalization by setting a Z score of 2 as the cutoff value. This resulted in an more straightforward classification of CBF reduction: type A (Z score ≤ 2) and type B (Z score >2). Postoperative hyperperfusion occurred only in type B but not in type A. This difference was statistically significant. In addition, 3D-SSP analysis with normalization demonstrated a higher predictive value and specificity for hyperperfusion than that without normalization. Furthermore, even the final patient in type B demonstrated a CBF increase \geq 50%. Therefore, the 3D-SSP image with normalization allowed easier recognition of patients at risk for hyperperfusion after CEA than without normalization.

3D-SSP searches gray matter activity along 13.5 mm from the cortical surface. The depth of the search was optimized to cover the entire gray matter, including that in a deep sulcus.¹⁰ On functional brain images that have a limited spatial resolution, 3D-SSP does not undersample either surface or sulcus gray matter activity; rather, it permits uniform unbiased sampling of gray matter activity. In fact, regional gray matter activity at surface and the depth of a sulcus can never be separated on SPECT images that have very high intercorrelation among neighboring pixels. This property of SPECT images also guarantees that neither surface nor depth of a sulcus is preferentially sampled by the 3D-SSP method. However, 3D-SSP cannot sample activity in the insula, putamen, and globus pallidus. Blood flow changes in these structures need to be evaluated by ROI analysis on transaxial slices. Thus, 3D-SSP and slice-based analysis can be used complementarily.

Conclusions

The present study suggests that 3D-SSP and normal control database provide a reliable and objective assessment of cortical CBF abnormalities. Severe reduction in CBF enables us to further distinguish patients at risk among those suspected to be at risk for hyperperfusion because of CVR impairment. Furthermore, 3D-SSP with normalization demonstrates a higher predictive value and higher specificity for postoperative hyperperfusion than 3D-SSP without normalization. This approach seems to be applicable to other cerebrovascular diseases such as ICA occlusion.

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