ORIGINAL

Evaluation of cerebral blood flow reserve in patients with cerebrovascular disease by SPECT using technetium-99m-L, L-ethyl cysteinate dimer

Ayuko Hori*, Masafumi Harada*, Hiromu Nishitani*, and Masaaki Uno**

**Department of Radiology, and **Department of Neurosurgery, The University of Tokushima School of Medicine, Tokushima, Japan*

Abstract : A technique for measuring the resting and acetazolamide (Acz)-activated cerebral blood flow without blood sampling by consecutive single-photon emission computed tomography (SPECT) using technetium-99m-L, L-ethyl cysteinate dimer (^{99m}Tc-ECD), called the ^{99m}Tc-ECD-RVR method, was recently developed by Matsuda *et al*. and Takeuchi *et al*. We evaluated the cerebral blood flow reserve in 77 patients with cerebrovascular diseases and 24 controls using this method. Baseline mean CBF (mCBF) was calculated from the application of Patlak plot graphical analysis with radionuclide angiography, and quantitative regional CBF (rCBF) images were obtained from qualitative axial SPECT images by the mCBF and Lassen's linearization correction. The activated SPECT images were obtained by subtraction of the first image from the second image. The mean increment ratio (IR) by calculating the mean CBF for the pre- and post-Acz in the controls was 1.26±0.12 (mean± SD). In patients with cerebrovascular disease, the reduction of the mean IR and regional IR was parallel with the degree of stenosis. This noninvasive method was also considered to be useful in evaluating the change in the hemodynamic reserve in cerebrovascular disease. J. Med. Invest. 49 : 134-141, 2002

Keywords : *99mTc-ECD, brain perfusion SPECT, acetazolamide, cerebral blood flow reserve*

INTRODUCTION

Acetazolamide (Diamox, hereafter)-activated brain perfusion SPECT is widely used for evaluation of the cerebral blood flow reserve (1). By conventional qualitative imaging, it is difficult to evaluate bilateral lesions and the cerebral blood flow reserve. Matsuda *et al*. developed a noninvasive measurement method of regional cerebral blood flow by a single RI angiography and two consecutive SPECT before and after acetazolamide (Acz) activation using technetium-99m-L, L-ethyl cysteinate dimer(^{99m}Tc-ECD) (2). This method was modified by Takeuchi *et al*. (3, 4) (ECD-RVR method), and it was widely accepted as a simple evaluation method of the cerebral blood flow reserve. Since the increase in blood flow after Acz activation varies considerably even among healthy individuals, the criterion of a significant increase in blood flow has not been established. In this study, we re-examined this method using patients with lesions in main arteries, and evaluated the hemodynamics before and after surgery.

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Address correspondence and reprint requests to Ayuko Hori, M.D., Ph.D., Department of Radiology, The University of Tokushima School of Medicine, Kuramoto-cho, Tokushima 770-8503, Japan and Fax : +81-88-633-7174.

PATIENTS AND METHODS

The subjects consisted of 63 patients in whom lesions in carotid arteries or in middle cerebral arteries were suspected by MRI and stenose greater than 70% were confirmed by DSA and Doppler ultrasonography, and 24 control subjects, including patients without significant stenosis and healthy volunteers. Thirteen patients were examined by SPECT before and after surgery. Of the 63 patients, 18 had stenosis or occlusion in bilateral internal carotid arteries, 14 had unilateral internal carotid artery occlusion, 18 had unilateral internal carotid artery stenosis, and 13 had stenosis or occlusion in unilateral middle cerebral artery. Fourteen patients with stenosis in vertebral arteries were also examined for comparison. The age of subjects ranged from 24-77 years with a mean of 60.8 years. There were no differences in age distribution between the groups.

Examination was performed according to the method of Takeuchi *et al*. (Fig. 1) (3, 4). After administration of ^{99m}Tc-ECD, RI angiography and SPECT imaging were performed. After Acz activation and the second administration of ^{99m}Tc-ECD, SPECT imaging was performed again. The SPECT data after activation were corrected for attenuation and subtracted from the SPECT data before activation. The same dose of ^{99m}Tc-ECD (555-740 MBq) was used for both resting and activated examinations.

1) RI angiography

RI angiography was performed using an apparatus (GCA901A, Toshiba Inc.) with a high resolution collimator for low energy and a 128×128 matrix. Ninety frames were collected at a speed of 1 frame/second.

2) SPECT

Imaging was performed using a 3-detector SPECT apparatus (PRISM3000, Picker Inc.) with fanbeam collimators for low energy. The imaging condition was 24 steps every 5 degrees, 10 sec/view, and a 64×64 matrix. The data were ramped using a data processor (ODYSSEY 750) with a low pass filter (Butterworth, Order 8.1, Cut-off 0.26 cycle/ pixel), and corrected by Chang's absorption correction (absorption correction coefficient, 0.09).

3)Quantitative images

The mean cerebral blood flow (mCBF) at rest was determined using the Patlak Plot method of Matsuda *et al*.(5). Using Lassen's linear correction with a single correction coefficient (α=2.59), regional cerebral blood flow (rCBF) before activation was determined (6, 7). The mean SPECT counts before and after activation were determined using 2 slices at the basal ganglia as controls and mCBF after activation was calculated from the above mCBF at rest using Lassen's correction method. Regional CBF after activation was determined by the method described above, and quantitative images were made.

4) Evaluation

Using mCBF before and after activation, the mean increment ratio (mIR=post-mCBF/pre-mCBF) was determined. The regional increment ratio (rIR) was determined by averaging rIR (post-rCBF/pre-rCBF) obtained from 10 regions of interest in each hemisphere. Statistical analysis was by ANOVA.

RESULTS

1) Group without significant stenosis

Table 1 shows the results of 7 healthy volunteers and 17 individuals without abnormalities determined by CT, MRI, and DSA (8 males, 16 females, 30-68 years, mean 53.1 years). The post-mIR was 1.26± 0.12 (mean±SD). There were no significant differ-

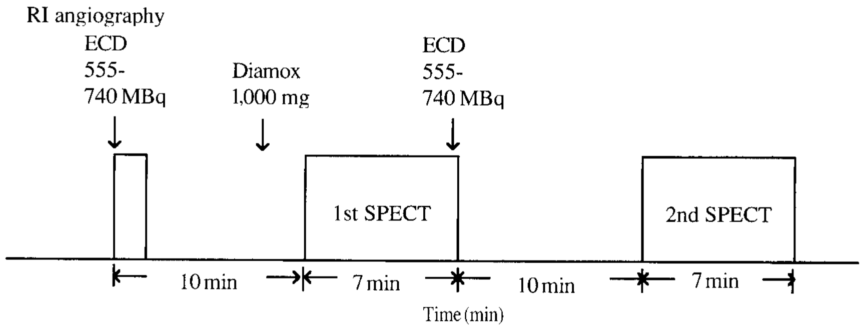

Fig. 1. Study protocol. Radionuclide angiography was performed immediately after intravenous bolus injection of 555-740 MBq of ^{99m}Tc-ECD, followed by the single-photon emission computed tomography (SPECT) imaging before and after acetazolamide (Acz) administration. Immediately after the completion of the first SPECT acquisition, 555-740 MBq of ^{99m}Tc-ECD was injected after Acz administration, and later the second SPECT acquisition was started.

Table 1. The values of mCBF and increment ratio in the normal control group

mCBF	45.7±6.1	44.8±6.5	(ml/100 g/min)
post ACZ	57.4±8.9		(ml/100 g/min)
mIR	1.26±0.12		
rIR	1.23±0.12	1.26±0.17	

CBF=cerebral blood flow, mCBF=mean CBF, ACZ=acetazoramide, IR=increment ratio, mIR=mean IR, rIR=regional IR

ences in mCBF or rIR between the right and left arteries.

2) Comparison in 5 groups with stenosis

Table 2 shows the mCBF and mIR in the 5 groups. Group 1 (n=18) : patients with stenosis or occlusion in bilateral internal carotid arteries ; group 2 (n=32) : patients with occlusion (n=14) or stenosis (n=18) in unilateral internal carotid artery ; group 3 (n=13) : patients with stenosis or occlusion in unilateral middle cerebral artery ; group 4 (n=24) : control group ; group 5 (n=14) : patients with stenosis in vertebral arteries. The pre- and post-mCBF and mIR were significantly lower in the bilateral lesion group, and the mIR was significantly lower in the group showing lesions in the middle cerebral arteries.

Comparisons of the rIR in the 4 groups, excluding the group showing lesions in the vertebral artery, showed significantly lower values in the bilateral lesion group and the group showing lesions in the middle cerebral arteries, while the rIR in the unilateral lesion group was similar to that of the control group (Fig. 2).

In the unilateral lesion group, the rIR was significantly lower in the stenosis subgroup than in the occlusion subgroup (Fig. 3).

3) Comparisons between the affected lesion and unaffected sides

There were no significant differences in the mCBF and rIR between the lesion and less-or non-affected sides in the bilateral lesion group, unilateral occlusion, or stenosis subgroups, and the group showing lesions in the middle cerebral artery.

Table 2. The mCBF and mIR values in 5 groups

Group	Vascular lesions		mCBF (ml/100 g/min) Unaffected side	Affected side	Activated	mIR
1	Bilateral ICA	(n=18)	40.3±3.1 *	* 39.2±3.6	46.0±6.5	1.14
2	Unilateral ICA	(n=32)	41.7±5.2	40.8±4.6	51.1±10.8	1.22 *
3	MCA	(n=13)	42.1±4.7	42.1±5.0	45.6±9.0 *	1.08 *
4	Controls	(n=24)	45.7±6.1 *	* 44.8±6.5 *	57.4±8.9 *	1.26 *
5	VA	(n=14)	40.5±6.3	39.6±5.6 *	47.7±9.1	1.18

CBF, cerebral blood flow ; mCBF, mean CBF ; IR, increment ratio ; mIR, mean IR ; ICA, internal carotid artery ; MCA, middle cerebral artery ; VA, vertebral artery
*significant at 95% by ANOVA

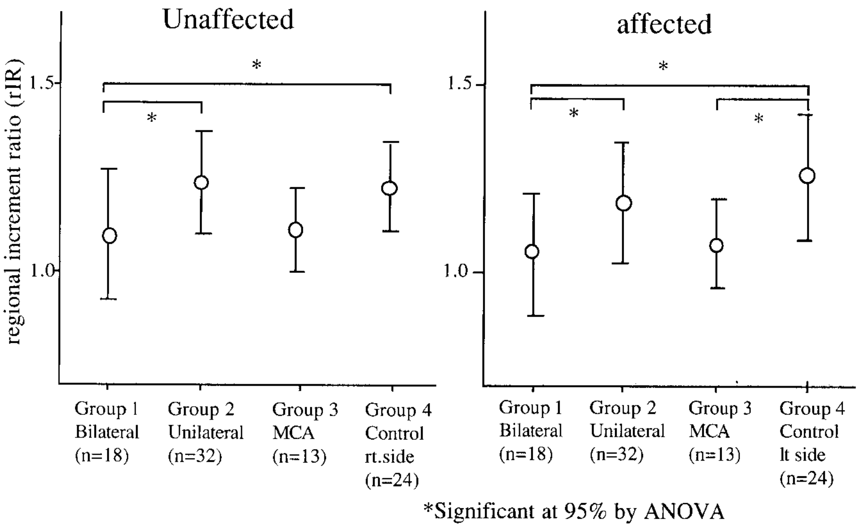

Fig. 2. Comparison of the regional increment ratio (rIR) in four groups.

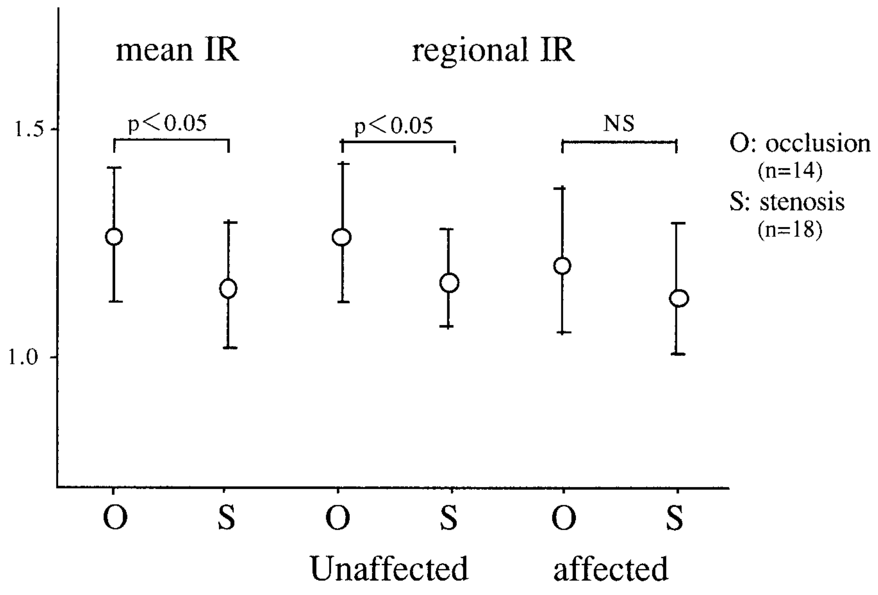

Fig. 3. Comparison of the mean increment ratio (mIR) and regional increment ratio (rIR) in the groups with unilateral ICA occlusion or stenosis.

4) Comparisons between pre- and post-surgery

In 6 patients with bilateral lesions, comparisons were made between before and after EC/IC bypass surgery. Of the 6 patients, mCBF increased in 2 patients after surgery, while mIR increased in 4 patients (Table 3). Of the 7 patients with unilateral lesions who underwent abrasion of carotid endarterectomy or bypass surgery, mCBF increased in 4 patients after surgery, while mIR increased only in 2 patients (Table 4).

CASE REPORTS

1) Patient 1

A 73-year-old male had occlusion in the right internal carotid artery and stenosis in the left internal carotid artery. He has had a history of atrial fibrillation and hypertension. The patient occasionally has had symptoms of transient ischemic attack (TIA) for several years, but remained untreated because no abnormalities had been detected by close examination. However, the symptoms became frequent, and multiple cerebral infarction, occlusion in the right internal carotid artery, and stenosis in the left internal carotid artery were detected on MRI. Brain perfusion SPECT revealed that the blood flow was markedly reduced after activation in the right cerebral hemisphere, especially in the area from the frontal lobe to the parietal lobe (Fig. 4AB). The %mIR value was 20%, and each rIR was low on the right side. Brain perfusion SPECT performed 2 weeks after surgical anastomosis of the right superficial temporal artery and the middle cerebral artery showed improvement in the blood flow in the right cerebral hemisphere. There was no significant difference in the blood flow between the right and left hemispheres. The same result was obtained after activation (Fig. 4CD). The %mIR value was 28%, and each rIR was improved.

Table 3. The mCBF and mIR values in six patients before and after STA-MCA anastomosis

Patient			Pre-operation			Post-operation		
			mCBF			mCBF		
			unaffected	affected	mIR	unaffected	affected	mIR
1	H.K	73 M	39.9	40.4	1.20	39.1	38.9	1.28
2	K.N	46 M	38.3	39.0	0.80	29.5	25.7	0.90
3	M.S	70 M	36.6	35.9	1.07	40.8	39.7	0.87
4	S.N	71 M	36.3	33.2	1.09	35.8	35.1	1.17
5	M.M	64 M	39.1	37.3	1.31	38.7	37.8	1.37
6	Y.F	68 M	41.1	40.0	1.23	45.6	42.6	1.14

CBF, cerebral blood flow; mCBF, mean CBF; IR, increment ratio; mIR, mean IR; STA-MCA, superficial temporal artery-middle cerebral artery

Table 4. The mCBF and mIR values in seven patients before and after endarterectomy

Patient			Pre-operation			Post-operation		
			mCBF			mCBF		
			Unaffected	Affected	mIR	Unaffected	Affected	mIR
1	F.T	47 M	44.7	44.3	1.11	39.5	38.7	1.49
2	N.K	65 M	45.0	42.5	1.33	40.0	41.0	1.11
3	T.Y	54 M	40.2	42.2	1.22	51.3	47.5	1.14
4	U.M	73 F	32.5	34.2	1.19	39.4	39.0	1.11
5	T.K	58 M	38.5	36.6	0.97	41.7	38.8	0.91
6	F.N	64 F	52.5	49.9	1.48	55.4	58.3	1.34
7	K.M	68 F	51.4	48.7	1.16	48.8	49.3	1.21

CBF, cerebral blood flow ; mCBF, mean CBF ; IR, increment ratio ; mIR, mean IR

2) Patient 2

A 62-year-old female with stenosis in the left middle cerebral artery. Paresis appeared on the right side about 2 years previously, and the disease was diagnosed as stenosis in the left middle cerebral atery and the patient was receiving conservative treatment. The patient visited our hospital after undergoing a TIA. Brain perfusion SPECT revealed that the accumulation after activation was very low in the left middle cerebral artery (Fig. 5AB). The %mIR value was 20%, while rIR was low in the area of low accumulation. The patient underwent surgical anastomosis of the right superficial temporal artery and the middle cerebral artery, and was re-examined by brain perfusion SPECT (Fig. 5CD). The blood flow before activation was markedly improved. After activation, the accumulation was slightly low in the left middle cerebral artery, but the mIR was significantly improved.

DISCUSSION

Qualitative imaging using Acz-activated brain perfusion SPECT is suitable for detecting right-left differences, but it is often difficult to evaluate bilateral lesions, treatment effects before and after operation, and condition changes during the follow-up period. Quantitative examination is better for evaluation of the effects of activation on the cerebral blood flow reserve. The method of Hashikawa *et al*. (6) using ^{123}I-IMP which shows good resultant blood flow is superior to other methods in the quantitive aspect, but its use is limited to specialized hospitals because it requires dynamic SPECT and continuous arterial blood collection. Recently, there a study reported using the IMP-ARG method (9) which is expected to be a simple quantification method, but arterial blood collection is still required in that method. On the other hand, the method used in the present stuby, which noninvasively measures regional cerebral blood flow at rest and upon activation in one day using ^{99m}Tc-ECD, does not require arterial blood collection, and most gamma-cameras can be used. Therefore, this method is considered suitable for routine examination. A drawback of this method is that it relies on Lassen's linear correction to compensate for the poor blood flow following ^{99m}Tc-ECD. Since RI angiography is omitted in this method on the basis of the use of subtraction, mCBF upon activation is calculated using Lassen's equation, and the same equation is used for determination of rCBF. The feasibility of this protocol was suggested to be convincing enough for a routinely performed clinical SPECT study to examine the vascular reserve (2-4).

The increase in blood flow may be overestimated when this method has not been established. In the present study, the %mIR value in the group without significant stenosis was 26%. Matsuda *et al*. reported the average %mIR value was 35.7% in demented patients without vascular disorders (2), and Takeuchi *et al*. reported %mIR values of 37 unaffected hemispheres and of 45 patients were 32% and 40%, respectively (3, 4). Therefore, Takeuchi *et al*. suggested that an mIR greater than 8% was significant (3). The increase in mCBF on the unaffected side was reported to demonstrate 44.5-59.5% by ^{123}I-IMP SPECT studies (8, 10), and approximately 30% by ^{133}Xe-SPECT studies (11). ^{99m}Tc-HMPAO property would not be favorable to the sensitive detection of flow increase because of its flow-limited extraction efficacy and initial back diffusion, and only 10% of radioactivity increase reported by Matsuda *et al* (12). Since accurate quantification is not always possible by the method used, it **is necessary to evaluate the reproducibility. Acetazolamide** does not directly affect cerebral blood vessels, but

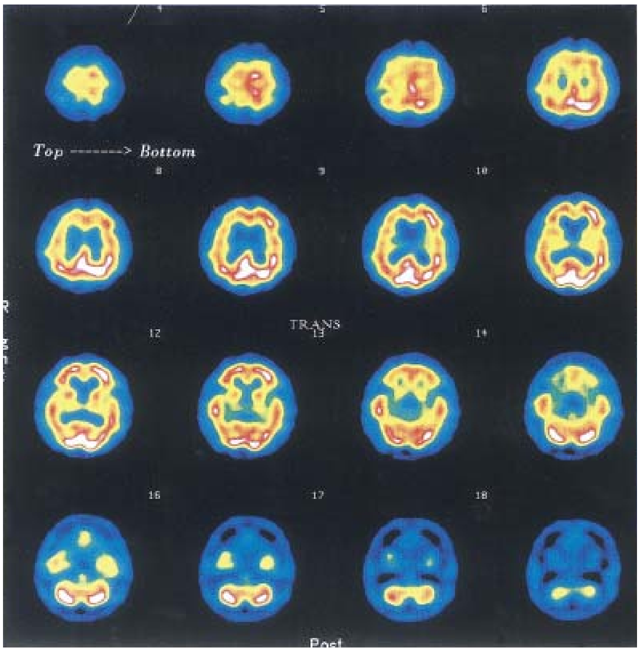

Figure 4 A

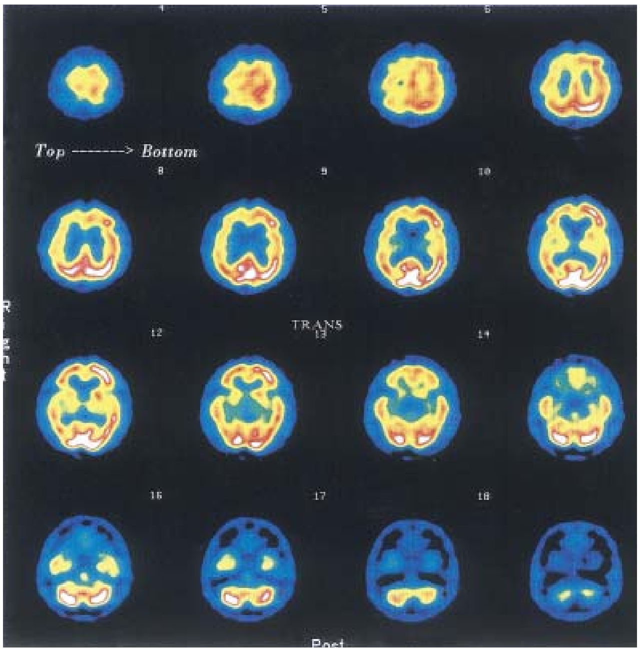

Figure 4 B

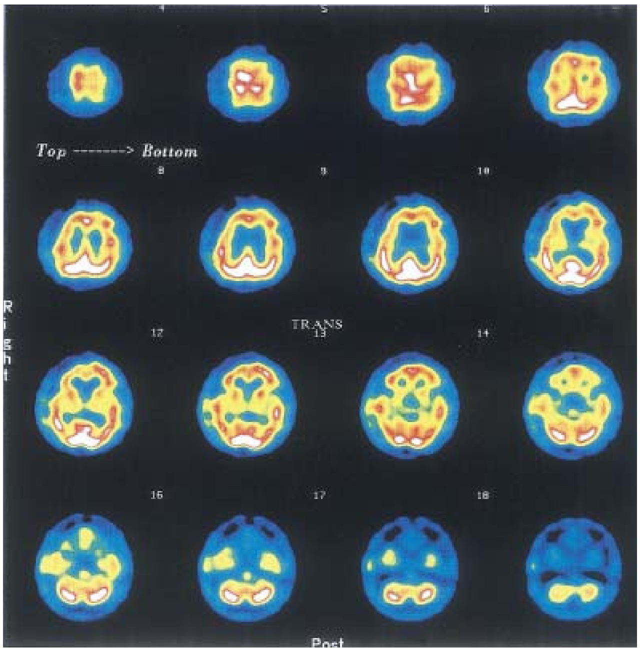

Figure 4 C

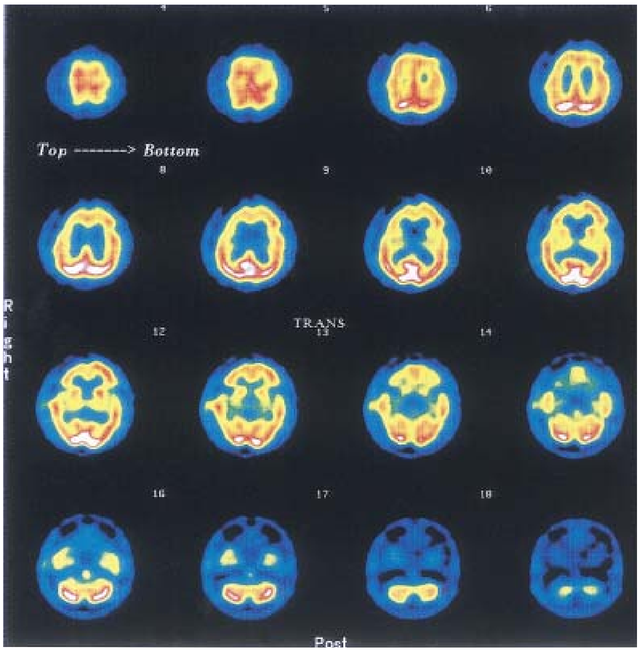

Figure 4 D

Figure 4 (A-D) : Case 1 73 y.o. Male
All are quantitative brain perfusion SPECT images and the regional CBF (rCBF) values of each ROI and the regional IR (rIR) of each rCBF are shown.
Figure 4 AB : Pre-operative brain perfusion SPECT (A : baseline, B : after ACZ) revealed that the blood flow and rIR were clearly reduced after activation in the right cerebral hemisphere.
Figure 4 CD : Post-operative brain perfusion SPECT (C : baseline, D : after ACZ) performed 2 weeks after the operation showed improvement in the blood flow in the right cerebral hemisphere. The increment ratios were also improved.

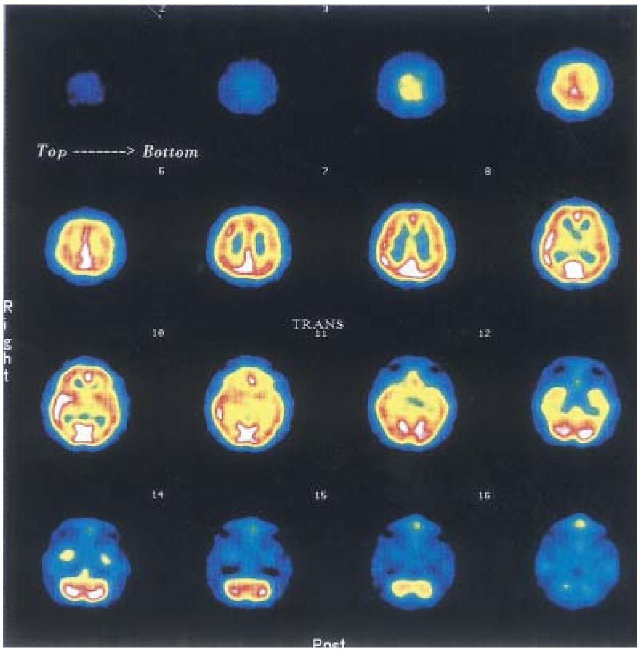

Figure 5 A

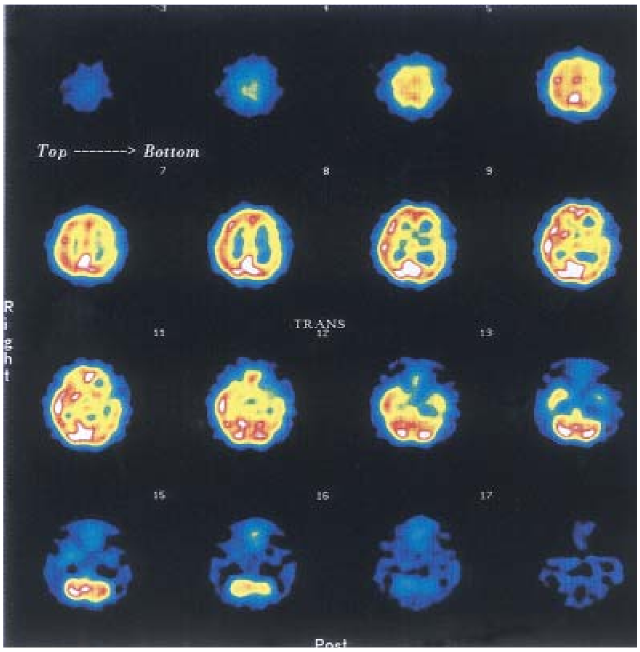

Figure 5 B

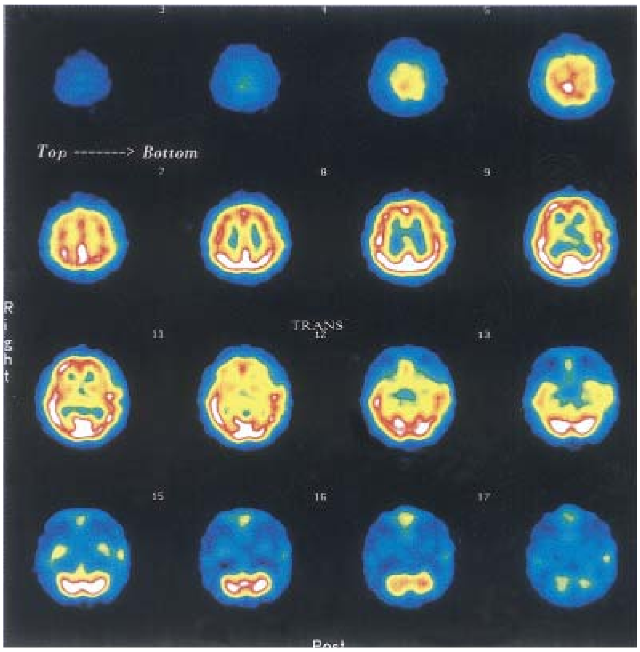

Figure 5 C

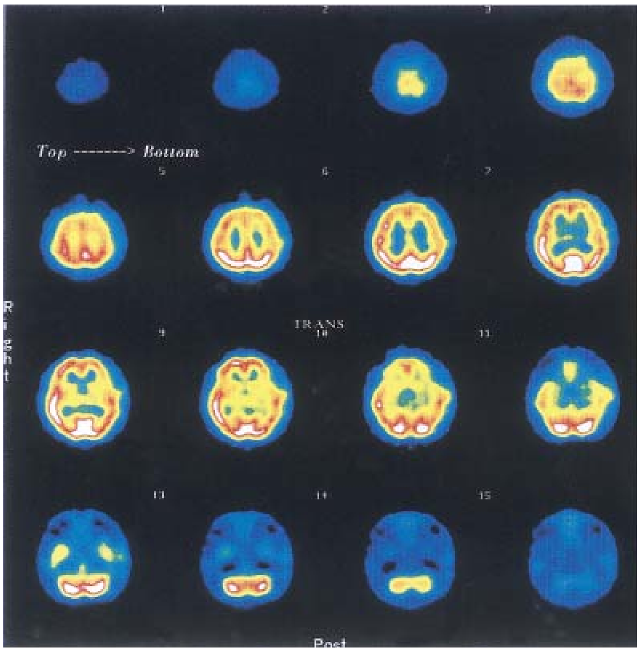

Figure 5 D

Figure 5 (A-D) : Case 2 62 y.o. Female
All are quantitative brain perfusion SPECT images and the regional CBF (rCBF) values of each ROI and the regional IR (rIR) of each rCBF are shown.
Figure 5 AB : Pre-operative brain perfusion SPECT (A : baseline, B : after ACZ) revealed that the accumulation after activation was very low in the left middle cerebral artery. The rIR were also low in the area of low accumulation.
Figure 5 CD : Post-operative brain perfusion SPECT (C : baseline, D : after ACZ) : The blood flow before activation was clearly improved. After activation, the accumulation was slightly low in the left middle cerebral artery, but the increment ratios were clearly improved.

blood flow is increased by elevation of regional carbon concentration. Although this method has these problems, the percentage obtained corresponded with the results of other studies.

Both mCBF and mIR were significantly lower in the bilateral lesion group, while only mIR was siginificantly lower in the group showing lesions in the unilateral artery, the mIR was significantly lower in the patients with stenosis than in the patients with occlusion. Blood flow on the stenosis side does not always parallel the degree of the stenosis depending on the degree of development of collateral blood vessels, but it was considered that the cerebral blood flow reserve could be evaluated by this method.

It was difficult to detect significant differences between before and after surgery because the number of patients was small and evaluation was made only immediately after the operation. However, blood flow increased in some of patients, suggesting that this method is useful for the comparison of the cerebral blood flow reserve between before and after operations and subsequent follow-up observations.

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