Regional Cerebral Blood Flow Measurement with Iodine-123-IMP Autoradiography: Normal Values, Reproducibility and Sensitivity to Hypoperfusion

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We recently proposed a simplified technique for measuring regional cerebral blood flow (rCBF) using the [^{123}I]N-isopropyl-p-iodoamphetamine (IMP) autoradiographic (ARG) method with SPECT (the IMP-ARG method). We examined normal values of rCBF and the reproducibility and sensitivity to hypoperfusion in stroke patients using this method. **Methods:** By using a standard arterial input, a single static scan, a fixed distribution volume (V_d) and one-point arterial blood sampling, we measured rCBF in 39 normal volunteers (19 men and 20 women; mean ages 61 ± 11 yr for the men and 60 ± 12 yr for the women). Eighteen neurologically stable patients with prior stroke (mean age = 65 ± 11 yr) were studied twice at a mean interval of 97 days. In 16 patients (7 men and 9 women, mean age = 63 ± 5 yr) with subarachnoid hemorrhage, rCBF was measured 1–2 wk after onset. Cerebral vasospasm was evaluated by repeated angiography. The mean rCBF in the vasospastic area was compared with that in a nonvasospastic area. **Results:** The mean rCBFs of the cerebral cortex and centrum semiovale in the volunteers were 33.0 ± 5.1 ml/100 g/min and 25.0 ± 4.5 ml/100 g/min, respectively. There was no age-dependent change in rCBF, but the women showed significantly higher cortical rCBF than the men ($p < 0.05$). In the stroke patients, the whole-brain CBF values showed high reproducibility, with high correlations between those obtained at the first and second studies ($y = -3.5 + 1.03x$; $r = 0.90$; $p < 0.001$). In the subarachnoid hemorrhage patients, the vasospastic area showed significantly lower rCBF than the normal cortical rCBF ($p < 0.01$) and the nonvasospastic area ($p < 0.01$). Brain regions with rCBF levels below 20 ml/100 g/min showed infarction on the follow-up CT scan. **Conclusion:** The IMP-ARG method is reproducible, sensitive to hypoperfusion and feasible for the quantitative evaluation of rCBF in routine clinical practice.

Key Words: SPECT; iodine-123-IMP; cerebral blood flow; cerebral infarction; subarachnoid hemorrhage

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Regional cerebral blood flow (rCBF) is a key parameter in determining the severity of ischemic brain damage when a cerebral artery is occluded. There is a cutoff threshold of rCBF, below which the brain tissue develops infarction (*1*). Although MRI has visualized abnormal brain perfusion immediately after ischemic insults (*2,3*), a perfusion image using a radiotracer technique, when feasible for routine clinical use, affords great advantages: reveals the magnitude of hypoperfusion (*4*), monitors response to therapy (*5*) and predicts clinical outcome (*6*). Iodine-123-N-isopropyl-p-iodoamphetamine (IMP) with SPECT has been used for this purpose (*7–10*). In the quantification of rCBF, however, the technique requires sequential data acquisition by dynamic SPECT scanning after the IMP infusion, continuous withdrawing or frequent sampling of arterial blood and separation of the lipophilic fractions of the blood samples. Because of these laborious procedures, the clinical applicability of the IMP method is still limited.

Recently, we proposed a simplified technique, the IMP-autoradiographic (ARG) method, which requires only one-point arterial blood sampling and the acquisition of a single static scan. The IMP-ARG method is based on the two-compartment model for tracer kinetics (*11,12*). The method uses a standard arterial input calibrated by the radioactivity of a single arterial whole blood sample, a standard lipophilic fraction of IMP in whole blood and a fixed distribution volume (V_d) of IMP. Previous studies indicated a good correlation between rCBF measured by PET with $H_2{}^{15}O$ and that measured by this method (*12,13*).

The objective of this study was to test the clinical applicability of the IMP-ARG method in a routine clinical setting. We first validated several assumptions pertaining to the IMP-ARG method that have not been analyzed in any previous study.

We assessed whether there were age and sex differences in the lipophilic fraction of IMP in whole blood and distribution volume of IMP in brain tissue. We then measured normal values of rCBF in 39 normal volunteers, the reproducibility of the CBF measurement in stroke patients and the sensitivity to hypoperfusion in vasospastic patients with subarachnoid hemorrhage (SAH).

MATERIALS AND METHODS

Calculation of rCBF

The rCBF is estimated by the IMP-ARG method, which has been previously described in detail (*12*). Briefly, the two-compartment model is used to describe the kinetics of IMP in the brain. The radioactivity concentration in the brain at time t after administration, $C_t(t)$, is given by:

$$C_t(t) = K1\ C_a(t) \otimes e^{-k2t}, \qquad \text{Eq. 1}$$

where $C_a(t)$ is the radioactivity of IMP in the lipophilic fraction at time t. Instead of measuring the input function in each patient by frequent blood sampling, we predetermined the standard input function of lipophilic IMP by measuring the mean lipophilic count of 12 normal volunteers independently from the present normal group. In this study of normal volunteers and patients, a sample of arterial whole blood was taken at 10 min after injection. The lipophilic IMP radioactivity in the blood was calculated by multiplying the whole-blood radioactivity by the mean lipophilic fraction (=0.70 in the previous study). The calculated radioactivity of lipophilic IMP was then used to calibrate the standard input function. K_1 and k_2 denote the rate constants of IMP influx and efflux, respectively, through the capillary membrane, and ⊗ is the convolution integral. K_1 and k_2 are also defined in relation to rCBF as follows:

$$K_1 = \rho E f \qquad \text{Eq. 2a}$$

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$$k_2 = f/\lambda, \quad \text{Eq. 2b}$$

where ρ is the density of brain tissue, E is the first-pass extraction fraction, f is rCBF and λ is the blood-brain partition coefficient of IMP. The distribution volume (V_d) of IMP is defined as the ratio of the influx rate to the efflux rate, and is thus:

$$V_d = \rho E \lambda. \quad \text{Eq. 3}$$

Substituting Equations 2a, 2b and 3 into Equation 1 and assuming E = 1.0, we obtain the tissue radioactivity at 40 min after injection as follows:

$$C_t(40) = \rho f C_a(t) \otimes e^{-40(\rho f/V_d)} \quad \text{Eq. 4}$$

When it is assumed ρ = 1.04 g/ml and V_d = 35.0 ml/g (mean value of whole brain measured in this study), Equation 4 provides the relationship between $C_t(40)$ and rCBF. Using this equation, a table of SPECT counts at the midscan time of 40 min is produced as a function of rCBF. Pixel-by-pixel rCBF values are then obtained through the table look-up procedure using the calculated table.

Validation of the Model Assumptions

Age and Sex Dependency of Lipophilic Fraction. The mean value of the lipophilic fraction in a whole-blood sample at 10 min after administration was 0.70 in the previous study (*12*). We analyzed the age and sex dependency of the lipophilic fraction in 15 normal volunteers [9 men, 50 ± 21 yr, and 6 women, 55 ± 11 yr (mean age ± 1 s.d.)]. The octanol fraction of IMP was estimated according to the method of Kuhl et al. (*8*).

Distribution Volume. In 10 normal volunteers (6 men and 4 women; 52 ± 13 yr), V_d was calculated by using IMP images obtained at 40 min and 180 min, a standard input function calibrated by the whole-blood radioactivity sampled at 10 min after injection and the mean lipophilic fraction at that time (*12*). A large oval region of interest (ROI) encompassing a whole-brain slice was set on the V_d image passing through the basal ganglia in each subject to determine the V_d for the whole brain. This value was used for the calculation of rCBF for the normal volunteers and the patients. The whole-brain V_d and regional V_d for the cerebral cortex, cerebellum, basal ganglia and centrum semiovale were analyzed in relation to age and sex.

SPECT Procedure

SPECT studies were performed using a ring-type SPECT scanner, a Headtome-SET080 (Shimadzu Corp., Kyoto, Japan), which provides 31 tomographic images simultaneously. The spatial resolution of the scanner is 13 mm FWHM at the center of the field of view, and the slice thickness was 25 mm FWHM at the field of view center. Image slices were taken at 5 mm center-to-center spacing parallel to the orbitomeatal line.

After a 1-min intravenous infusion of 111 MBq of [^{123}I]IMP (5-ml volume) at a constant rate of 5 ml/min and a 1-min infusion of physiological saline at the same rate, data acquisition with a low-energy, all-purpose collimator was initiated at 30 min after the IMP administration for a scan duration of 20 min (midscan time = 40 min).

The images were reconstructed using the weighted-filtered backprojection technique, in which the attenuation correction was made by detecting the edge of the object. The attenuation coefficient of 0.065 cm^{-1}, a Butterworth filter (cutoff = 0.45 Nyquist; order = 3) and a ramp filter were used for image reconstruction.

One milliliter of arterial blood was taken from the brachial artery at 10–12 min post-IMP administration. The whole-blood radioactivity was measured using a well counter cross-calibrated with SPECT. The arterial partial pressures of O_2 and CO_2, hematocrit and blood pH were also measured in a blood gas tension analyzer. The arterial hemoglobin concentration and the fraction of oxyhemoglobin were measured with a hemoglobin analyzer (MLK-1100; Nihon Koden Ltd., Tokyo, Japan). The mean arterial hemoglobin concentration was significantly lower in the women (11.6 ± 1.0 g/dl) than in the men (14.1 ± 1.7 g/dl, $p < 0.01$). There was no significant difference between the men and women in other parameters.

Setting of ROIs

We selected five tomographic slices obtained at 14, 41, 54, 68 and 80 mm above the orbitomeatal line and parallel to it. Circular ROIs of 16-mm diameter were set in the following brain structures: the cerebellar cortex, cerebellar vermis, pons, superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus, superior temporal gyrus, middle temporal gyrus, inferior temporal gyrus, insular cortex, inferior parietal lobule (angular and supramarginal gyrus), somato-sensory cortex, superior occipital gyrus, occipital cuneus, cingulate gyrus, parahippocampal gyrus, head of the caudate nucleus, lentiform nucleus, thalamus and centrum semiovale. In the identification of these brain structures on the SPECT images, the CT scan and the brain atlas of Matsui and Hirano (*14*) were used. The mean cortical CBF was calculated by averaging the rCBF for the cortical ROI of the frontal, temporal, parietal and occipital lobes in each subject.

Normal Volunteers

We studied 19 male and 20 female normal volunteers to measure the normal values of rCBF by the IMP-ARG method. The men ranged in age from 38 to 82 yr (mean, 60.5 ± 10.8 yr). The women ranged in age from 40 to 79 yr (mean, 59.8 ± 11.5 yr). Screening of normal health status included a medical review of past history, a physical examination and neurological and mental tests. Subjects having a past history of hypertension, diabetes mellitus or atrial fibrillation were excluded. The laboratory studies included a complete blood count to screen for hematological disease; serum electrolytes (Na, K, Cl), creatinine and blood urea nitrogen to screen for renal disease; fasting blood glucose, total cholesterol, triglyceride and uric acid to screen for metabolic disease; and total plasma protein and albumin, bilirubin, alkaline phosphatase, serum glutamic oxaloacetic transaminase, serum glutamic pyruvate transaminase, creatinine phosphokinase and γ-glutamyl transpeptidase to screen for liver disease. Before the SPECT study, unenhanced cranial CT scan was performed using a GE/9800 scanner to rule out organic lesions of the brain. Subjects with leukoaraiosis and/or asymptomatic lacunar infarction were excluded from the SPECT study. rCBF values for the entire group, for men and for women were separately analyzed in relation to age.

Stroke Patients

The first patient group studied consisted of eight patients with cerebral infarction, seven patients with unilateral subcortical hemorrhage and three patients with SAH (14 men and 4 women; mean age, 64.7 ± 10.6 yr). They were studied twice during the follow-up period. Their rCBF values were analyzed to test the reproducibility of the method. The first measurement was performed 3 mo or more after the onset. The mean interval between the first and the second study was 97 ± 93 days. All patients were neurologically and psychologically stable during the interval. The difference in PaC_{O_2} between the first and the second study was not corrected.

The second patient group consisted of 16 patients (7 men and 9 women; mean age, 63.1 ± 5.2 yr) with SAH due to rupture of an intracranial aneurysm confirmed at the first angiography. The patient information is summarized in Table 1. All of the patients had surgical clipping of the aneurysm the day of onset (Day 0). rCBF was measured on days 6–11 (mean, day 8.4). Eight patients showed neurological symptoms at this time of SPECT study. None of the patients showed brain infarction on CT at this time. The

TABLE 1
Patient Information

Patient no.	Age (yr)	Sex	Location of aneurysm	Clinical symptom	Vasospasm on SPECT study	Day of SPECT	Cerebral infarction after SPECT study
1	60	M	Left ICA	Consciousness disturbance	(++) left ACA (++) left MCA	11	+
2	56	M	AComA	Right hemiparesis	(++) left MCA (++) bilateral ACA	6	−
3	77	F	AComA	None	(+) bilateral ACA	10	−
4	70	F	Right ICA	Left occulomotor palsy	(+) right MCA	7	−
5	50	F	Right MCA	None	(+) right MCA	6	−
6	74	M	Right ICA	Motor aphasia	(+) left MCA	8	−
7	79	F	AComA	Motor aphasia	(+) left MCA	8	−
8	69	M	AComA	Tetraplegia	(++) bilateral MCA (++) bilateral ACA	8	+
9	73	F	AComA	None	(+) bilateral ACA	10	−
10	59	F	AComA	None	(+) bilateral ACA	6	−
11	52	M	AComA	None	(+) bilateral ACA	10	−
12	72	F	Left ICA	None	(+) left MCA	10	−
13	51	M	Right ACA	Left hemiparesis	(+) right MCA	9	−
14	49	F	Left ICA	Right hemiparesis	(+) left MCA	7	−
15	61	F	Right ACA	None	(+) bilateral ACA	9	−
16	58	M	AComA	None	(+) bilateral ACA	9	−

ICA = internal carotid artery; AComA = anterior communicating artery; ACA = anterior cerebral artery; MCA = middle cerebral artery; (++) = a reduction in arterial diameter exceeding 50%; (+) = a reduction between 25% and 50%; M = male; F = female.

second angiography was performed 1 or 2 days before or after the SPECT study. The vasospasm was detected by comparing the second set of angiography with the first one. The degree of vasospasm was defined as follows: a reduction in arterial diameter exceeding 50% was considered severe vasospasm, a reduction between 25% and 50% was considered mild vasospasm and a reduction of less than 25% was not considered vasospasm. A circular ROI of 16-mm diameter was set in the hypoperfused cortical region in the territory of the vasospastic arteries and in the nonvasospastic cortical region. The mean rCBF in the vasospastic area was compared with that in the nonvasospastic area and also with the normal value obtained in the 20 age- and sex-matched normal volunteers.

RESULTS

Methodological Validations in Normal Volunteers

Lipophilic Fraction. The mean lipophilic fractions of IMP in the arterial blood at 10 min for 15 subjects, for 9 men and for 6 women were 0.721 ± 0.026, 0.725 ± 0.030 and 0.716 ± 0.021, respectively. There was no significant difference between the values in the men and women. Figure 1 shows the lipophilic fraction in each subject plotted against the subject's age. Neither age- nor sex-dependent change was found. The mean lipophilic fraction measured in the previous study was 0.702 ± 0.031 and not significantly different from those obtained for 15 subjects, for men and for women in this study. The lipophilic fraction of 0.70 was used for the rCBF calculation for the volunteers and the patients in this study.

Distribution Volume. The mean V_d for the whole brain was 35.0 ± 3.0 ml/g in 10 normal volunteers (34.3 ± 2.9 ml/g for men and 35.6 ± 3.1 ml/g for women). There was no sex difference in the whole-brain V_d. Figure 2 shows the whole brain V_d value in each subject plotted against his or her age. There was no significant age-dependent difference in the whole-brain V_d in either the men or women.

In 10 normal volunteers, the mean V_d values for the cerebral cortex, cerebellum, basal ganglia and centrum semiovale were 37.5 ± 3.6, 37.9 ± 3.8, 40.6 ± 3.9 and 35.7 ± 3.5 ml/g, respectively. There was a significant difference between the V_d of the basal ganglia and that of the centrum semiovale ($p < 0.05$) and between the mean V_d for the whole brain and that for the basal ganglia ($p < 0.05$). No significant difference was found between men and women for the V_d in any brain region analyzed, nor was there any age-dependent difference in the V_d value in any regions.

Normal Values

The averaged rCBF values for all subjects, for men and for women are shown in Table 2. The mean rCBFs of the cerebral cortex and centrum semiovale were 33.0 ± 5.1 ml/100 g/min and 25.0 ± 4.5 ml/100 g/min, respectively. The women showed significantly higher rCBF than the men in all brain structures ($p < 0.05$ or less). The occipital cuneus showed the highest

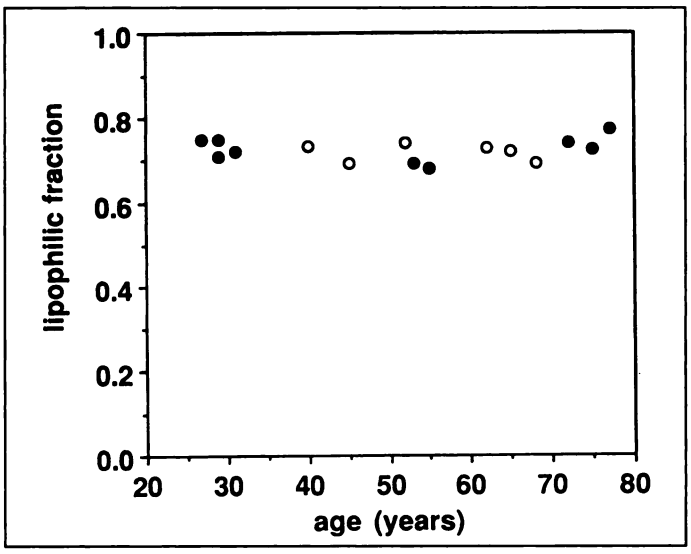

FIGURE 1. Lipophilic fraction of IMP in the arterial whole blood at around 10 min after intravenous administration is plotted against the ages of each of nine men (●) and six women (○). No age-dependent change in lipophilic fraction was found.

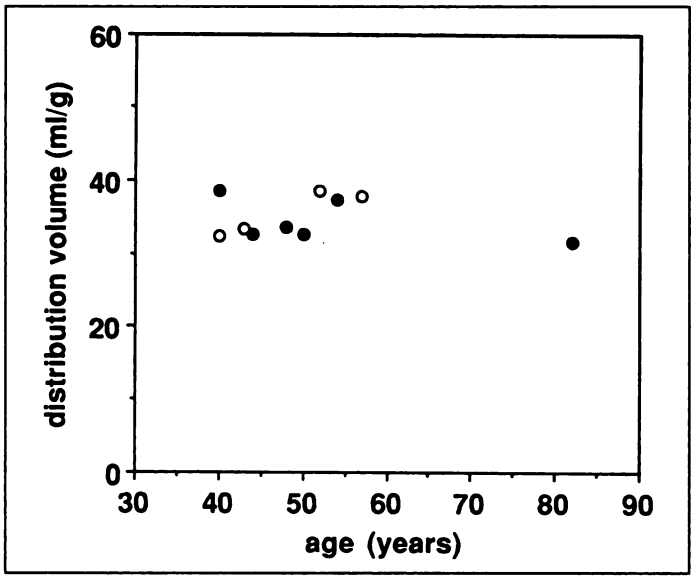

FIGURE 2. Whole-brain V_d of IMP is plotted against the ages of six men (●) and four women (○). There was no significant age-dependent change in whole-brain V_d.

value among the brain structures, followed by the thalamus, cerebellar cortex and putamen. There was no right-to-left hemisphere asymmetry. Among the cerebral cortices, the parahippocampal gyri showed the lowest value. The mean ratios of CBF for cortical gray matter to that for white matter (centrum semiovale) were 1.46 ± 0.21 for men and 1.44 ± 0.18 for women.

In Figure 3, the mean cortical and mean white matter rCBF for each subject are plotted against age. No significant change associated with age was found in the cortex or in any brain structures. Figure 4 illustrates the rCBF images for the male and female subject who had the closest rCBF values to the mean for each sex.

Stroke Patient Study

Reproducibility in Patients with Prior Stroke. In Figure 5, the whole-brain CBF values acquired during the first measurement are plotted against those acquired during the second measurement for 18 patients. The mean PaC_{O_2} values at the first and the second measurement were 38.0 ± 2.8 mmHg and 38.5 ± 3.2 mmHg, respectively. Significant correlation between the first and the second measurements ($y = -3.54 + 1.03x$; $r = 0.90$; $p < 0.001$) was observed.

Sensitivity to Hypoperfusion in SAH Patients. The mean rCBF in the vasospastic cortical area (23.6 ± 6.2 ml/100 g/min)

TABLE 2
Mean Values of rCBF for 39 Normal Volunteers Measured by Iodine-123-IMP-ARG Method

Regions		rCBF (ml/100g/min) Total (n = 39)	Men (n = 19)	Women (n = 20)
Posterior fossa structures				
Cerebellum	Right	36.5 ± 6.2	33.9 ± 5.6	39.2 ± 5.6
	Left	36.2 ± 5.9	33.5 ± 5.1	38.8 ± 5.5
Cerebellar vermis	Right	35.6 ± 6.2	32.8 ± 4.8	38.3 ± 6.2
	Left	36.3 ± 6.4	33.6 ± 5.3	38.9 ± 6.4
Pontine nuclei		34.3 ± 5.6	32.6 ± 5.7	36.1 ± 5.1
Supratentorial structures				
Cortical gray matter				
Superior frontal gyrus	Right	32.0 ± 5.1	30.2 ± 4.4	33.8 ± 5.1
	Left	31.1 ± 6.3	28.7 ± 5.0	33.5 ± 6.6
Middle frontal gyrus	Right	32.4 ± 5.8	30.0 ± 4.8	34.9 ± 5.7
	Left	32.5 ± 5.8	30.4 ± 5.0	34.6 ± 5.9
Inferior frontal gyrus	Right	32.8 ± 5.7	30.4 ± 4.3	35.3 ± 6.0
	Left	32.2 ± 5.4	30.1 ± 4.5	34.4 ± 5.6
Superior temporal gyrus	Right	30.4 ± 5.4	28.1 ± 4.1	32.8 ± 5.6
	Left	29.4 ± 4.9	27.3 ± 3.8	31.5 ± 5.1
Middle temporal gyrus	Right	32.2 ± 5.6	30.4 ± 5.5	34.1 ± 5.2
	Left	30.6 ± 4.7	28.7 ± 4.1	32.4 ± 4.5
Interior temporal gyrus	Right	30.5 ± 4.8	28.7 ± 4.1	32.3 ± 4.9
	Left	30.0 ± 4.8	28.3 ± 4.3	31.6 ± 4.8
Insular cortex	Right	33.3 ± 6.3	30.6 ± 5.5	36.1 ± 6.0
	Left	33.2 ± 6.6	30.1 ± 4.8	36.3 ± 6.8
Inferior parietal lobule	Right	32.9 ± 5.6	30.7 ± 4.6	35.2 ± 5.7
	Left	32.3 ± 5.5	30.4 ± 5.1	34.2 ± 5.5
Somato-sensory cortex	Right	32.8 ± 6.0	30.3 ± 5.1	35.2 ± 5.9
	Left	32.1 ± 5.8	29.9 ± 4.5	34.2 ± 6.1
Parahippocampal gyrus	Right	28.3 ± 4.7	26.5 ± 3.6	30.1 ± 5.1
	Left	28.4 ± 4.9	26.5 ± 4.0	30.2 ± 5.0
Superior occipital gyrus	Right	35.5 ± 5.7	33.3 ± 5.2	37.7 ± 5.5
	Left	35.8 ± 6.0	33.3 ± 4.7	38.3 ± 6.1
Occipital cuneus	Right	36.8 ± 7.6	33.7 ± 6.6	39.9 ± 7.5
	Left	36.3 ± 7.1	33.7 ± 6.2	38.9 ± 7.2
Cingulate gyrus	Right	34.0 ± 6.9	31.2 ± 5.6	36.9 ± 6.9
	Left	32.8 ± 6.6	30.2 ± 5.1	35.4 ± 7.0
Central gray matter				
Caudate nucleus	Right	34.7 ± 6.3	32.1 ± 5.2	37.2 ± 6.3
	Left	35.3 ± 7.4	32.8 ± 6.0	37.9 ± 7.9
Putamen	Right	36.0 ± 6.2	33.4 ± 5.0	38.6 ± 6.3
	Left	36.8 ± 6.8	34.2 ± 5.5	37.9 ± 7.1
Thalamus	Right	38.1 ± 7.8	34.7 ± 5.8	41.5 ± 8.1
	Left	37.6 ± 7.1	34.9 ± 6.5	40.3 ± 6.9
White matter				
Centrum semiovale	Right	25.1 ± 4.5	23.5 ± 3.9	26.7 ± 4.6
	Left	24.8 ± 4.4	23.0 ± 3.7	26.6 ± 4.4

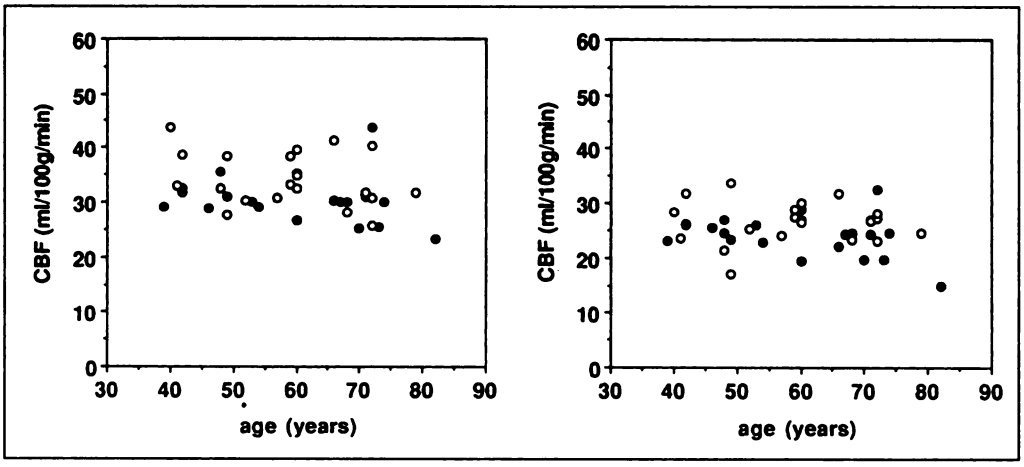

FIGURE 3. Mean cortical rCBF values (left) and white matter rCBF (right) values for 19 men (●) and 20 women (○) are plotted against their age. No significant age-dependent changes were observed for entire men or women. Note that the rCBF values for women are generally higher than those for men at any given age.

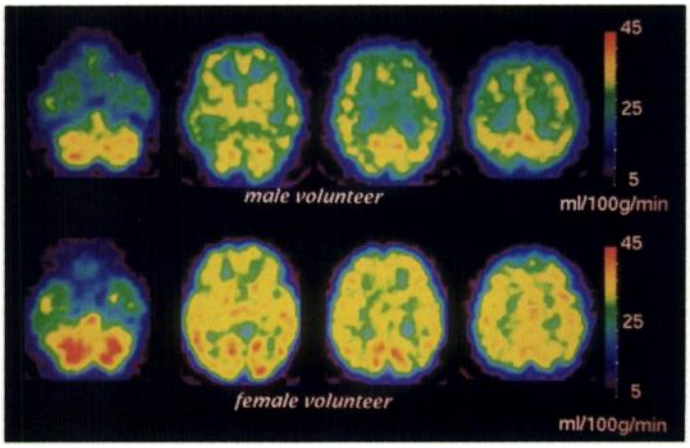

FIGURE 4. rCBF images obtained by the IMP-ARG method from the male (upper) and female (lower) normal volunteers whose rCBF values were closest to the mean for their sex. The peak of the color scale was seen at 45 ml/100 g/min for both subjects.

was significantly lower than the control cortical rCBF (33.2 ± 5.1 ml/100 g/min) ($p < 0.01$) and the rCBF of nonvasospastic territory (37.4 ± 6.1 ml/100 g/min) ($p < 0.01$). In eight symptomatic patients, the rCBF of the vasospastic cortical area was 22.4 ± 4.2 ml/100 g/min, and it was 25.6 ± 6.4 ml/100 g/min in asymptomatic patients. These values were not statistically different.

In Figure 6, the rCBF in the vasospastic area is plotted against the day after onset. On the follow-up CT scans, cerebral infarction was found in the brain area with rCBF levels of 13.9 ml/100 g/min in Patient 8 and of 19.4 ml/100 g/min in Patient 1. No vasospastic lesion with rCBF value of more than 20 ml/100 g/min showed cerebral infarction. In Patient 7, who showed diffuse hypoperfusion in the territories of bilateral anterior cerebral arteries and the left middle cerebral artery, the rCBF was 23 ml/100 g/min (Fig. 7). No brain infarction was found on the follow-up CT scan. Figure 8 shows the rCBF images for Patient 8, who had local severe vasospasm. The patient was tetraplegic at the time of rCBF study. The lowest

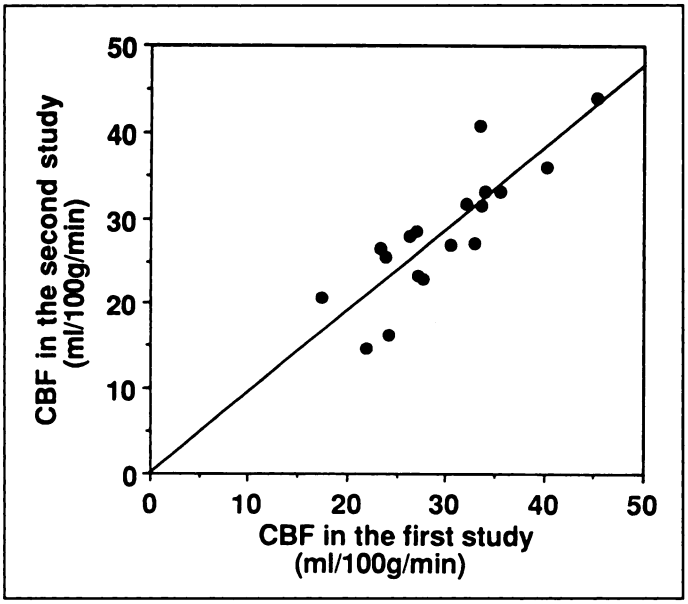

FIGURE 5. Whole-brain CBF values obtained during the second SPECT session are plotted against those obtained during the first SPECT measurement for 18 patients with previous stroke. There is a significant correlation between the first and the second measurement ($y = -3.54 + 1.03x$; $r = 0.90$; $p < 0.001$).

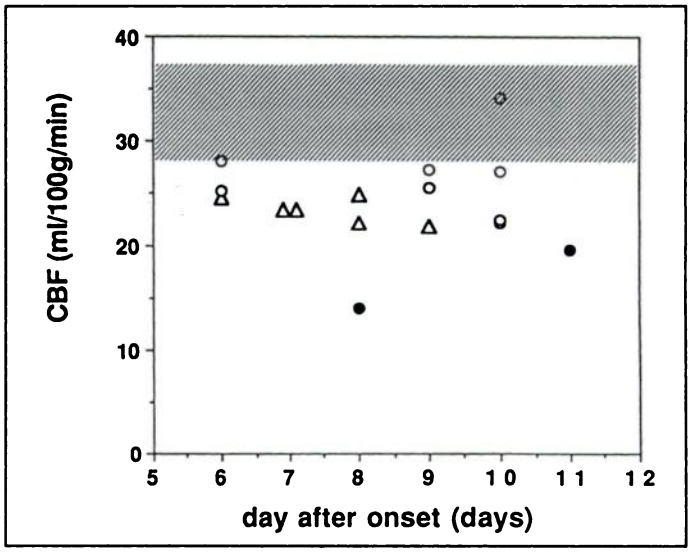

FIGURE 6. The rCBF value in the vasospastic area in each SAH patient is plotted against the day after onset. The shaded area indicates the range of mean cortical CBF and 1 s.d. obtained from 39 normal volunteers. Two symptomatic patients (●) showed cerebral infarction on the follow-up CT scan. In the other six symptomatic patients (△) and eight asymptomatic patients (○), no evidence of cerebral infarction due to vasospasm was found on follow-up CT.

CBF value, 13.9 ml/100 g/min, was in the territory of the right middle cerebral artery. Although the CT scan showed normodensity of the hypoperfused area visualized at the SPECT study, the area later showed infarction, as revealed at the follow-up CT study.

DISCUSSION

Validation of Model Assumptions

This study revealed that the lipophilic fraction of IMP and the V_d value were independent of age and sex. The use of a single value for these parameters for men and women and for younger and older individuals does not seem to result in any systematic error in rCBF calculation related to the age or sex.

The mean V_d value for the normal cortex was 37.5 ± 3.6 ml/g in this study, whereas it was 31.3 ± 3.0 ml/g in a previous study (*12*). This difference would result from the improved method of the attenuation correction. In this study, the attenuation correction was performed by detecting the edge of the brain in this study instead of assuming an elliptical brain outline. When the previous method was applied to the present data, the mean V_d value for the normal cortex was 30.8 ± 3.5 ml/g.

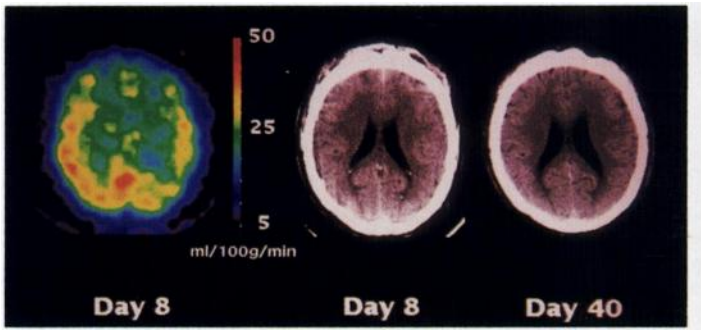

FIGURE 7. In Patient 7, the rCBF image (left) showed hypoperfusion in the territories of the bilateral anterior cerebral artery and left middle cerebral artery on Day 8, when motor aphasia was manifest. CT scan revealed no evidence of infarction (center). rCBF was 23 ml/100 g/min in the territories of vasospastic arteries. No brain infarction was found on the follow-up CT (right).

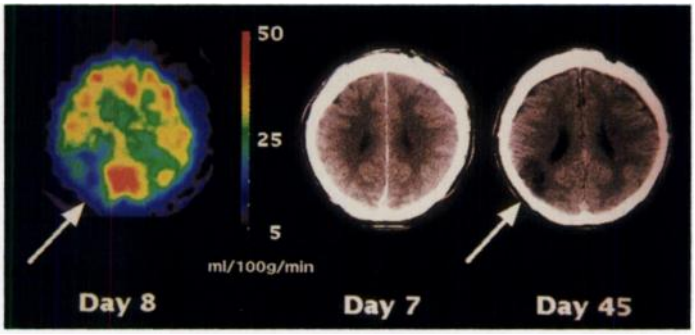

FIGURE 8. In Patient 8, the rCBF image (left) demonstrated severe hypoperfusion (13.9 ml/100 g/min) in the territory of the right middle cerebral artery at Day 8. The patient was tetraplegic. The CT image at day 7 (center) disclosed no evidence of infarction. The corresponding area later developed brain infarction (right).

The whole-brain V_d (35.0 ml/g) used to calculate rCBF was lower than the regional V_d values. This is due to the inclusion of the ventricles in the large ROI encompassing the whole-brain slice. The simulation study indicated 14% overestimation of rCBF for the basal ganglia (measured V_d = 40.6 ml/g), 7% for the cortex (37.5 ml/g), 8% for the cerebellum (37.8 ml/g) and 2% for the white matter (35.7 ml/g).

It remains unknown whether the fixed V_d is valid in the pathological brain. The V_d in complete cerebral infarction, indicated as a low-density lesion on CT scans, was reported to be 10.1 ml/g (*12*). In such lesions, the use of the fixed V_d (35.0 ml/g) resulted in an underestimation of rCBF by 10% when the rCBF was 7.7 ml/100 g/min. Iida et al. (*13*) recently compared the rCBF values obtained using the fixed V_d with those obtained using the measured V_d in normal volunteers, in patients with cerebrovascular disease and in patients with degenerative diseases. The results indicated a good correlation of the rCBF values obtained by the two methods. Although the V_d values obtained in the pathologic brain are not shown separately in their report, the fixed V_d does not seem to substantially reduce the accuracy of the IMP-ARG method.

As was found in the multicenter project (*13*), the V_d value is dependent on the spatial resolution and scatter component of the SPECT scanner. Therefore, the value should be measured for each scanner and for each reconstruction algorithm used.

rCBF Values in Normal Volunteers

The mean cortical CBF for the total group was 33.0 ml/100 g/min in this study. This value is considerably lower than obtained using other modalities (*15–17*). Lassen (*16*) reported that the cortical gray matter CBF was 80 ml/100 g/min, based on their measurement using ^{133}Xe. Using $H_2{}^{15}O$ bolus injection and a high-resolution PET scanner, we found normal cortical CBF of 56.3 ml/100 ml/min (*17*). Our previous study also revealed that the rCBF measured by the IMP-ARG method was underestimated by 33% when it was compared with PET $H_2{}^{15}O$ study in the same subjects. The limited spatial resolution of the SPECT scanner might be a main reason for the systematic underestimation of rCBF due to the partial volume effect. This underestimation would also be induced by the limited first-pass extraction (E) of IMP. We assumed E to be unity, whereas Kuhl et al. estimated the extraction to be 0.92 and 0.74 for hemispheric rCBF of 33 and 66 ml/100 g/min, respectively (*8*).

Age and Sex Differences

We did not find age dependency of rCBF in any brain regions examined in this study. Because age dependency of V_d and lipophilic fraction were not observed, this result is not due to the use of fixed V_d value and lipophilic fraction in the IMP-ARG method. Reported studies are inconclusive regarding the effect of age on rCBF (*18–20*). That we failed to find it in this study might be due to the selection of normal volunteers. As demonstrated by Duara et al. (*21*), the cerebral glucose metabolic rate was independent of age in stringently screened normal volunteers. The set of criteria of normal health status used in this study was compatible with that in the study by Duara et al (*21*). Our result indicated that rCBF, like cerebral glucose metabolism, can be maintained even in the elderly individuals.

We found significant a sex difference in rCBF, but we also found no significant difference between men and women for the V_d and lipophilic fraction. Therefore, the higher rCBF in the women is not due to using the fixed values for V_d and lipophilic fraction. We also calculated cortical rCBF for men and women by using measured V_d for each sex (V_d = 34.3 for men and 35.6 for women). The mean cortical rCBF values were still significantly different. Sex difference in rCBF has been noted by several investigators using different methods (*22,23*). Thus, our result is consistent with the known sex difference for rCBF.

Reproducibility in Stroke Patients

The reproducibility of the method is critically important in routine clinical use. Podreka et al. (*9*) studied the correlation of the first and the second measurements of rCBF acquired at a 1-wk interval in 14 normal volunteers by dynamic IMP method with serial arterial blood sampling. The measurements were highly reproducible. In this study, we examined stroke patients in the chronic stage with stable neurological state. Although changes in the arterial partial pressure of CO_2 were not corrected, the correlation between the two sets of measurements was highly significant in spite of the much longer interval than that in the study by Podreka et al (*9*).

There is a possibility that the good reproducibility of this method partly resulted from the limited first-pass extraction of the tracer. In areas with increased rCBF, a large change in rCBF would be required to detect a change in signal. One should take into account that the IMP-ARG method is less sensitive to rCBF change in high-flow areas than in low-flow areas and that it is apparently reproducible in high-flow areas.

Sensitivity to Hypoperfusion

Reduction of rCBF due to vasospasm in SAH patients has been quantitatively measured. Voldby et al. (*24*) studied the relationship between the degree of vasospasm observed by angiography and rCBF in 38 SAH patients. They found that severe diffuse vasospasm, defined as a reduction in arterial caliber exceeding 50% in two or more arteries, was associated with significant reduction in rCBF. In this study, the rCBF in the territory of severe vasospasm was significantly lower than both the control value for the normal volunteers and that of the nonvasospastic territory in the SAH patients. This indicated that the IMP-ARG method is sensitive enough to detect hypoperfusion due to a steno-occlusive arterial lesion.

Powers et al. (*25*) demonstrated using PET, the critical flow level below which the brain tissue would develop infarction in patients with vasospasm due to SAH. Our results are consistent with theirs, although the critical rCBF level (20 ml/100 g/min) was higher than that shown in the PET measurement (12 ml/100 g/min). It may be possible to prospectively differentiate reversible from irreversible ischemia by determining the threshold of CBF infarction using the IMP-ARG method.

Limitations of the Method

The IMP-ARG method uses the standard arterial input function instead of the measurement of arterial radioactivity in each individual. Therefore, the main factor that limits the

accuracy is the individual difference of the input from the standard input. Iida et al. (*12*) demonstrated that the rCBF values calculated by means of the standard input were well correlated with those calculated by the individual input in a small group of subjects. Their recent study validated the use of a single standard input across institutions and in patients with various diseases (*13*). However, it is still possible that the standard input might be different from the actual one in patients with pathological conditions such as severe cardiac failure.

The rCBF has been measured after administration of acetazolamide to test the cerebral vasoreactivity (*26*). During the pharmacological intervention, systemic circulation might be altered. It remains unknown whether the IMP-ARG method is applicable in such trials.

CONCLUSION

After intravenous administration of IMP, one-point arterial blood sampling and a single SPECT scanning provide quantitative rCBF mapping on introduction of two-compartment analysis, a standard input function, fixed values of brain V_d and arterial lipophilic fraction of IMP. Although the rCBF values in normal volunteers were lower than those obtained by other techniques, the measurement seems feasible in the routine clinical setting, as it is reproducible and sensitive to hypoperfusion in stroke patients. The clinical application in SAH patients demonstrated the critical ischemic threshold, below which the brain tissue would later show infarction. Further validation of the standard input function in various pathological conditions and in pharmacological trials may improve the clinical applicability of the method.

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