Evaluation of a Double-Injection Method for Sequential Measurement of Cerebral Blood Flow with Iodine-123-Iodoamphetamine

Sadahiko Nishizawa, Yoshiharu Yonekura, Fumiko Tanaka, Toru Fujita, Shinsaku Tsuchimochi, Koichi Ishizu, Hidehiko Okazawa, Nagara Tamaki and Junji Konishi

Departments of Nuclear Medicine and Brain Pathophysiology, Kyoto University Faculty of Medicine, Kyoto, Japan

To test the feasibility of applying N-isopropyl-[^{123}I]p-iodoamphetamine (IMP) for sequential measurements of regional cerebral blood flow (rCBF) with injection of two separate doses in a single procedure, kinetic analysis based on a two-compartment model was done using dynamic SPECT data. A microsphere model analysis without consideration of IMP washout from the brain was also tested for clinical application. **Methods:** A dynamic SPECT scan consisting of fifty 1-min scans was obtained on 15 patients using a three-head rotating gamma camera with two separate doses of IMP (111 MBq each) at the beginning and 25 min after scan initiation. The reproducibility of two resting rCBF scans was tested in six patients and the cerebrovascular response shown by increased rCBF with acetazolamide (1 g) was assessed in nine patients. **Results:** Two-compartment model analysis showed excellent reproducibility of resting rCBF scans and significantly different cerebrovascular reactivity to acetazolamide between areas with and without ischemia. Microsphere model analysis showed smaller values in the first rCBF image by 3% and in the second by 10%, resulting in lower values for cerebrovascular reactivity. The difference in cerebrovascular reactivity between ischemic and nonischemic areas, however, is highly significant. **Conclusion:** The double-injection method for IMP is feasible for two sequential rCBF measurements in a single procedure and is applicable for acetazolamide challenge. Simple microsphere model analysis, as well as a two-compartment model analysis, provide reliable assessment for cerebrovascular reactivity despite the complex dynamics of IMP and are feasible for clinical application.

Key Words: iodine-123-iodoamphetamine; regional cerebral blood flow; cerebral perfusion reserve; compartmental analysis; single-photon emission computed tomography

J Nucl Med 1995; 36:1339–1345

It is important to assess cerebral perfusion reserve in patients with an occlusive disease of the major cerebral arteries to understand hemodynamic compromise and candidate selection for revascularization surgery (*1–3*). The cerebral perfusion reserve, which consists of complex parameters, can be assessed by testing cerebral vasodilatory capacity, or cerebral vascular reactivity, which is shown by an increase of regional cerebral blood flow (rCBF) with a cerebral vasodilative agent such as carbon dioxide or acetazolamide (ACZ) (*4–6*).

SPECT with ^{133}Xe is a well established method for rCBF quantification which is feasible for repeated measurements and sensitive enough to show a 30%–70% increase of rCBF with 1 g ACZ in normal subjects or unaffected hemispheres of a unilateral occlusive disease (*7–11*). Technetium-99m-hexamethylpropyleneamine oxime (^{99m}Tc- HMPAO) is well known for producing high quality SPECT images without a specialized SPECT device. The nonlinear relationship between rCBF and ^{99m}Tc-HMPAO uptake, especially at high blood flow rates, however, results in considerable underestimation of rCBF after ACZ challenge, showing an increase of 10%–30% in normal or unaffected brain regions (*12–14*) which may obscure the difference between normal and affected regions.

N-isopropyl-[^{123}I]p-iodoamphetamine ([^{123}I]IMP) is a potent cerebral perfusion tracer with high single-pass extraction by the brain and good linearity between its uptake and rCBF (*15,16*). Sequential measurements of rCBF by [^{123}I]IMP with a double-injection method in a single procedure, if possible, seem to offer great advantages to SPECT brain studies. The tracer dynamics of [^{123}I]IMP are, however, rather complex, showing continuous release of the tracer from the lung reservoir to the bloodstream and gradual washout from the brain, which preclude simple subtraction of the radioactivity due to the first dose from a second such as ^{99m}Tc-HMPAO SPECT.

To evaluate the feasibility of [^{123}I]IMP SPECT with a double-injection method for sequential measurements of rCBF in a single procedure, we performed a kinetic analysis based on a two-compartment model using dynamic SPECT, taking into consideration IMP washout from the brain. The analysis was done to test the reproducibility of

Received May 23, 1994; revision accepted Dec. 20, 1994.

For correspondence or reprints contact: Sadahiko Nishizawa, MD, Positron Imaging Laboratories, McConnell Brain Imaging Center, Montreal Neurological Institute, 3801 University St., Montreal, Quebec, Canada H3A 2B4.

two sequential rCBF measurements and to evaluate rCBF change after ACZ challenge. We compared the results with those calculated with a microsphere model that does not consider IMP washout from the brain but is easy to perform in the clinical setting. The cerebrovascular response (or rCBF change) to an ACZ challenge was also assessed from semiquantitative analysis of tissue radioactivity change.

METHODS

Patients

Two sequential measurements of rCBF using [^{123}I]IMP and SPECT with a double-injection method in a single procedure were performed on 15 patients. Six of them (mean age 61.3 yr), including four with an occlusive disease of the cerebral major arteries and two with suspected cerebrovascular disease later proven to be normal, were studied without ACZ challenge to assess the reproducibility of two sequential rCBF measurements. Cerebrovascular reactivity (or response) was assessed by measuring rCBF before and after an intravenous administration of ACZ (1 g) in nine patients (mean age 40.2 yr), including four with moyamoya disease, two with an occlusive disease of a unilateral internal carotid artery, two with an arteriovenous malformation and one with a brain tumor.

Data Acquisition

SPECT images were acquired with a three-headed rotating gamma camera (PRISM 3000, Picker International, Inc., Bedford Heights, OH) equipped with low-energy, high-resolution, fan-beam collimators that provide a spatial resolution of 8.0 mm FWHM at the center of the field of view with a sensitivity of 135 cps/MBq. The patient's head was placed in a semicylindrical headholder lined with a rubber sponge to prevent motion during the study. Data acquisition was performed in a continuous rotation mode with 40 steps in 120° and 1.5 sec/step, which translates into 1 min for one SPECT dataset. Clockwise and counterclockwise rotations for 120° were alternately carried out for 50 min, and 50 sequential 1-min SPECT datasets were obtained. To compensate for increased tracer concentration in the brain during a rotation, two or four sequential SPECT datasets were added for image reconstruction.

Two doses of 111 MBq [^{123}I]IMP were administered intravenously for 1 min at a constant rate with an infusion pump, one at the beginning and the other at 25 min after scan initiation. An arterial input function was obtained for each patient. Twenty-seven arterial blood samples were drawn from a small catheter placed on the brachial artery, initially every 15 sec and at gradually prolonged intervals for 20 min after each dose of [^{123}I]IMP. The concentration of unmetabolized [^{123}I]IMP was determined in 12 of the 27 samples by extraction with octanol for each dose. In nine patients, ACZ (1 g) was slowly administered intravenously for 1 min, starting 13 min after scan initiation. The time schedule for the whole procedure was summarized in Figure 1. All patients received potassium iodide (30 mg/day) for 4 days starting the day before the study to avoid the uptake of free radioactive iodine by the thyroid.

All SPECT images were reconstructed using a filtered back-projection algorithm with a ramp filter after prefiltering with a Butterworth filter (cutoff frequency of 0.25 and order 4). Attenuation correction was performed using Chang's method, assuming that the head is an ellipsoid shape with a uniform attenuation coefficient of 0.06/cm. For quantification of rCBF, cross-calibration between the SPECT scanner and the well counter was performed by scanning a 16-cm diameter cylindrical phantom containing ^{123}I solution of known concentration. Linearity between SPECT values and concentrations of the ^{123}I solution was confirmed using a 20-cm diameter cylindrical phantom containing six pie-shaped compartments with different concentrations of the ^{123}I solution.

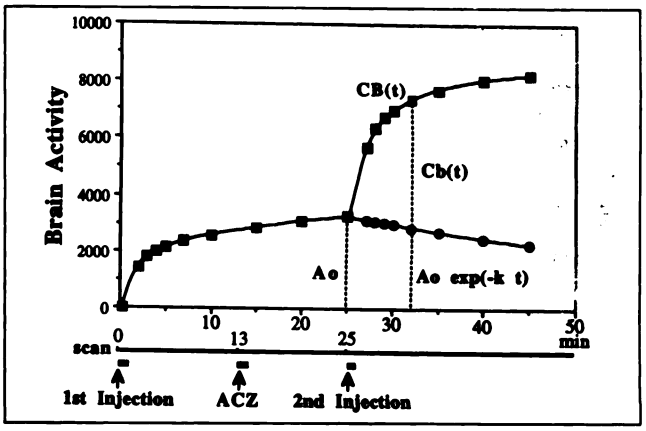

FIGURE 1. Typical time-activity curve of the brain in the double-injection method. The basic concept for the analysis is shown with the time course of the whole procedure (50 min) in the lower part of the figure. Ao = IMP concentration in the brain at the end of the first measurement; k = rate constant for washout from the brain to the blood; Cb(t) = IMP concentration in the brain for the second measurement; and CB(t) = total IMP concentration in the brain.

Kinetic Model and Data Manipulation

We used a two-compartment model for the tracer kinetics of [^{123}I]IMP in the brain as previously reported (*17*). Figure 1 shows a typical time-activity curve of the brain with two separate doses of [^{123}I]IMP according to the protocol of this study. The first rCBF ($rCBF_{1st}$) is estimated by a least-squares curve fitting procedure based on the two-compartment model expressed by the following differential equation:

$$dC_b(t)/dt = rCBF_{1st}\, E\, C_a(t) - k_{1st}\, C_b(t), \qquad \text{Eq. 1}$$

where $C_a(t)$ denotes a lipophilic tracer in the arterial blood, $C_b(t)$ is a tracer concentration in the brain, E is a single-pass extraction which is assumed as complete (E = 1) in this study, and k_{1st} is a washout rate constant from the brain to the blood for the first measurement. For the estimation of the second rCBF ($rCBF_{2nd}$), cerebral radioactivity due to the first dose should be subtracted from the total cerebral radioactivity. During the second measurement, a lipophilic tracer measured in the arterial blood is from both the first and the second dose which we cannot separate from each other. Because the rCBF and washout rate has already been altered, it is reasonable to consider that after arterial lipophilic tracer totally contributes to the second measurement of rCBF after the second [^{123}I]IMP administration, and the cerebral accumulation of [^{123}I]IMP due to the first dose up to the time of the second injection is washed out according to the washout rate of the second situation (k_{2nd}). Therefore, tracer accumulation for the second measurement in the brain after the second dose, $C_b(t)$, is:

$$C_b(t) = C_B(t) - A_0 \exp(-k_{2nd}(t - 25)), \qquad \text{Eq. 2}$$

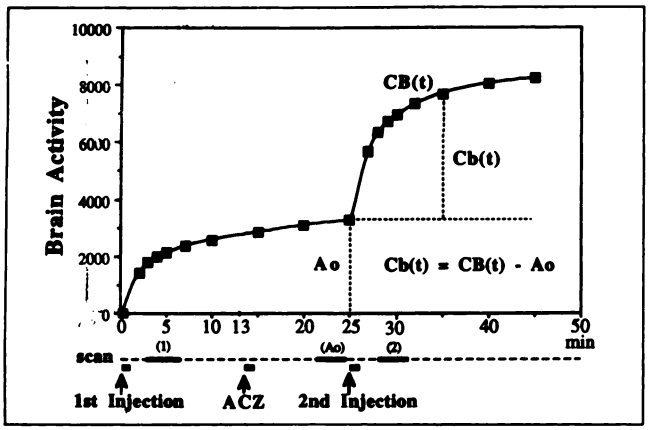

FIGURE 2. Schematic description for the microsphere model analysis. The second rCBF was calculated with simple subtraction of radioactivity from the first dose without considering the effect of washout. The time of the procedure is shown in the lower part of the figure. (1) = SPECT scan for the first rCBF; (2) = SPECT scan for the second rCBF; and (Ao) = SPECT scan just before the second dose.

where $C_B(t)$ is total cerebral radioactivity of [^{123}I]IMP in the brain and A_0 is the cerebral radioactivity due to the first dose just prior to administration of the second dose. Therefore, $rCBF_{2nd}$ and k_{2nd} can be also estimated based on the following after substituting Equation 2 to Equation 1 and integrating both sides:

$$C_B(t) - A_0 \exp(-k_{2nd}(t-25)) = rCBF_{2nd} \int_{25}^{t} C_a(u)du$$

$$- k_{2nd} \int_{25}^{t} (C_B(u) - A_0 \exp(-k_{2nd}(u-25)))du. \quad \text{Eq. 3}$$

The reproducibility and the response to ACZ is expressed as the percent change between the first and the second rCBF:

$$\%\ rCBF\ change = 100(rCBF_{2nd} - rCBF_{1st})/rCBF_{1st}.$$

Dynamic SPECT consisted of five 2-min SPECT scans for the first 10 min and three 4-min SPECT scans in each subsequent measurement. Because rCBF estimation largely depends on the early portion of the brain time-activity curve, we considered the effect of ACZ on the first measurement to be small and almost constant on the second.

The rCBF and percent rCBF change were also calculated based on the microsphere model (*16*), which does not take into consideration [^{123}I]IMP washout from the brain and is more easily applicable in a clinical setting. In this study, we evaluated a simple method for calculating the second rCBF by subtracting the radioactivity of first dose without considering washout effects (Fig. 2). For these measurements, SPECT data at 5 min after each injection of [^{123}I]IMP, which consisted of 4-min data, were used with a reference input function calculated by integrating an arterial input curve over 5 min. The simplest method to assess cerebrovascular reactivity without quantification using arterial sampling data also was evaluated. This method was based on the percent change of radioactivity (adjusted by injected dose) in each ROI between two measurements with simple subtraction without consideration of washout. We used the same radioactivity data as in the microsphere model analysis.

Data Analysis

Four large regions of interest (ROIs) ranging in size from 10 to 15 cm^2 were drawn freehand on the frontal and parietal lobes bilaterally in each case. These ROIs were placed on the cortices without cerebral infarction by referring to x-ray CT and/or MR images. In one patient without ACZ challenge who had a large cerebral infarction, we placed two ROIs on the unilateral frontal and parietal lobes without infarction. The reproducibility of two sequential rCBFs was assessed in six patients without ACZ challenge. The response to ACZ was assessed in nine patients. In the analysis of ACZ response, ROIs were classified into ischemic and nonischemic groups which were defined according to angiographic findings, whether or not there was severe stenosis or occlusion in major cerebral arteries perfusing the region and filling delay of the peripheral circulation without sufficient collateral vessels.

Statistical analysis was performed by a paired t-test for data with repeated measurements. Comparisons between ischemic and nonischemic groups were made by an independent t-test. Effects of multiple comparisons were corrected by the Bonferroni method. Regression analysis was also performed between two measurements and between two methods.

RESULTS

Two-compartment model analysis revealed good reproducibility of the two sequential rCBF measurements with 38.7 ± 5.4 (mean ± s.d.) ml/100 g/min for the first and 38.1 ± 6.3 ml/100 g/min for the second (Table 1). There was no difference in the washout rate between the two measurements. The response to ACZ was good in nonischemic areas with a 59.5% ± 11.6% increase but was poor in ischemic areas with 12.4% ± 16.2% increase (Table 2),

TABLE 1
The Reproducibility of Measured rCBF and Washout Rate [n = 6 (22 ROIs)]

Parameter	First measurement		Second measurement		% rCBF change
	rCBF	Washout rate	rCBF	Washout rate	
Two-compartment model	38.7 ± 5.4*	0.011 ± 0.003*	38.1 ± 6.3*	0.011 ± 0.003*	−1.6 ± 5.4
Microsphere model	37.5 ± 5.3†	—	34.4 ± 5.1†	—	−8.8 ± 4.7

*Without significant difference.
†With significant difference ($p < 0.01$).
rCBF: ml/100g/min. Washout rate: 1/min. Values are mean ± s.d.

TABLE 2
Response to Acetazolamide Challenge (n = 9)

Parameter	First measurement		Second measurement		% rCBF change
	rCBF	Washout rate	rCBF	Washout rate	
Two-compartment model					
Ischemic (15 ROIs)	41.1 ± 8.5†	0.012 ± 0.004	46.1 ± 11.1*†	0.015 ± 0.005*	12.4 ± 16.2*
Nonischemic (21 ROIs)	42.4 ± 7.8†	0.010 ± 0.004†	62.7 ± 10.0*†	0.020 ± 0.003*†	59.5 ± 11.6*
Microsphere model					
Ischemic (15 ROIs)	39.9 ± 8.1	—	40.4 ± 9.1*	—	1.1 ± 11.8*
Nonischemic (21 ROIs)	40.8 ± 6.9†	—	57.8 ± 8.3*†	—	42.4 ± 10.2*

*Significant difference between ischemic and nonischemic areas ($p < 0.01$).
†Significant difference between first and second measurement ($p < 0.01$).
rCBF = ml/100g/min. Washout rate = 1/min. Values are for mean ± s.d.

whereas both increases were significant ($p < 0.01$), and a significant difference was also seen between them ($p < 0.01$). Although a positive correlation was observed between rCBF and the washout rate (Fig. 3A), no difference was demonstrated in both resting rCBF and the washout rate in ischemic and nonischemic areas (Table 2, Fig. 3B).

Compared to the results of the kinetic analysis, microsphere model analysis showed lower values for the first rCBF measurement by about 3% and by about 10% for the second in patients with and without ACZ challenge. A linear relationship with a high correlation coefficient was demonstrated between rCBF measurements by both methods (Fig. 4). Although the response by the microsphere model analysis was somewhat small compared to the two-compartment model analysis (Table 2), the relationship between them was linear with a high correlation coefficient (Fig. 5). The difference between ischemic and nonischemic groups was also significant ($p < 0.01$).

The response calculated from the change in radioactivity in each ROI also showed a linear relationship to two-compartment model analysis results (Fig. 6), and a significant difference was seen between ischemic and nonischemic groups (18.5 ± 12.3 and 66.6 ± 13.6, respectively, $p < 0.01$).

DISCUSSION

By assessing rCBF alteration after a chemical or stress test compared with a resting test, one can potentially enhance the detection of mild or latent abnormalities of cerebral perfusion or metabolism (*18–21*). An ACZ challenge is one of the most popular tests for assessing cerebral perfusion reserve. ACZ induces cerebral vasodilatation within several minutes after an intravenous injection and the resultant augmentation of rCBF represents cerebral vasodilatory capacity. For precise assessment of rCBF change, the study should be performed in succession during a single procedure to ensure baseline rCBF stability and reproducibility of the measurement without movement of the patient's head. Quantitative assessment is also required, especially for patients with bilateral or severe hemodynamic compromise, because bilateral decrease of the response may obscure abnormalities if analyzed qualitatively.

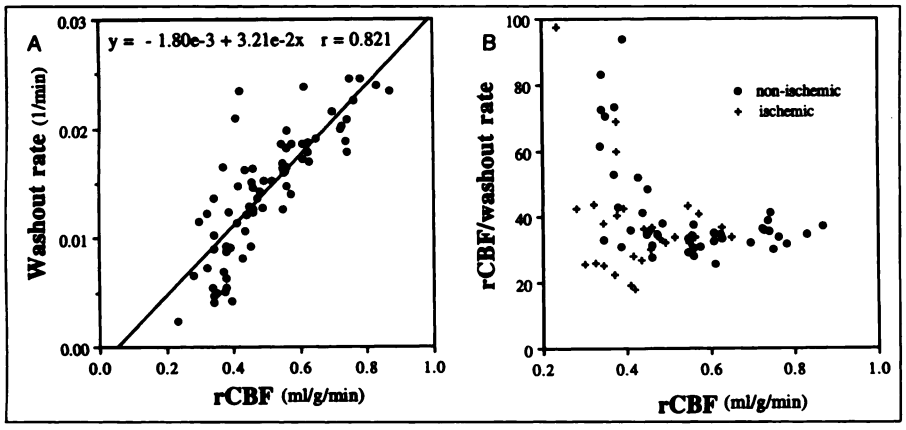

FIGURE 3. (A) Relationships between rCBF and washout rate and (B) rCBF and partition coefficient. A positive correlation is seen between rCBF and washout rate. The partition coefficient is almost constant regardless of rCBF, although considerable variations are at low blood flow rates for the ischemic and nonischemic regions, which seem to be due to the error caused by low radioactivity at the low flow rate.

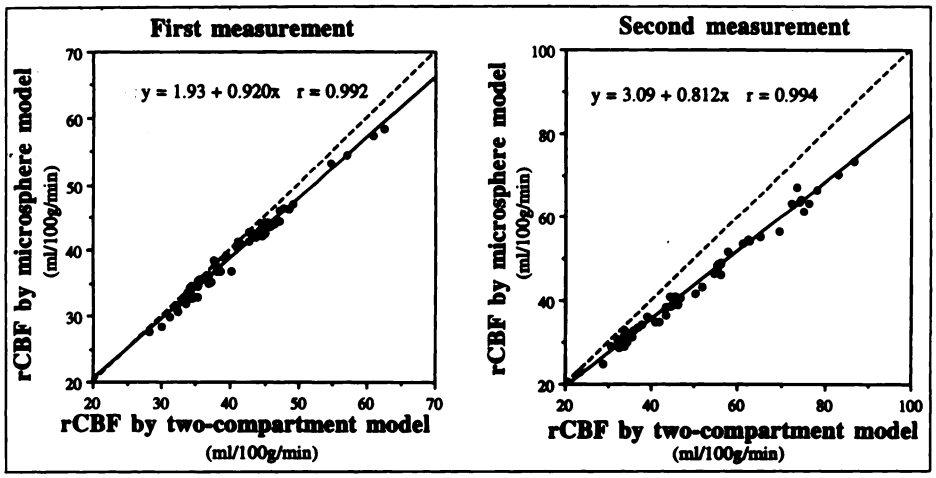

FIGURE 4. Relationship between rCBF estimated by two-compartment model analysis and microsphere model analysis. A linear relationship with a high correlation coefficient is observed in the first (left) and second (right) measurements. Microsphere model analysis yields smaller values for rCBF than two-compartment model analysis and the slope is steeper in the first measurement than in the second because the washout effect was neglected. The dotted line denotes the line of identity.

Iodine-123-IMP is a well established radiopharmaceutical for cerebral perfusion SPECT imaging with high single-pass extraction and excellent linearity between tracer uptake in the brain and rCBF with possible quantification of rCBF (*16,17,23,24*). In an attempt to obtain two rCBF measurements under different conditions, however, the rCBF studies were performed on separate days because of the complex dynamics of [^{123}I]IMP (*25,26*). Hashikawa et al. (*27*) used a microsphere model to show that a separate dose method of [^{123}I]IMP with subtraction of estimated radioactivity of the first dose permitted good reproducibility for sequential rCBF measurements and reasonable estimation of response to ACZ (*27*).

In this study, we analyzed the dynamics of two separate doses of [^{123}I]IMP based on a two-compartment model to determine two sequential rCBF measurements. A two-compartment model was initially described by Kuhl et al. (*16*), although they calculated rCBF in humans with a microsphere model using early SPECT data because of negligible washout in the initial phase. In previous studies reasonable estimation of rCBF was made by dynamic SPECT with two-compartment model analysis compared to rCBF measured by ^{15}O and PET (*24*) or calculated by the microsphere model at 5 min postinjection (*17*). In our attempt for sequential measurements of rCBF in a single procedure, the reproducibility of sequential rCBFs was excellent with a two-compartment model analysis and was comparable to that by ^{133}Xe and SPECT or ^{15}O and PET (*28–30*). In addition, the response to ACZ in nonischemic areas was also as good as that in normal or nonaffected brain assessed by ^{133}Xe and SPECT.

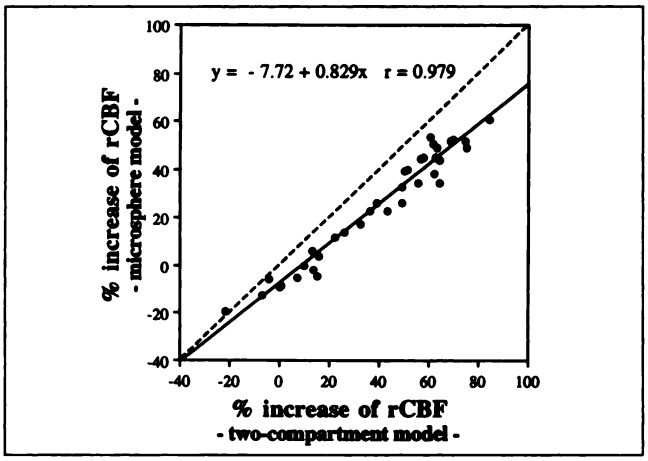

FIGURE 5. Relationship between two-compartment model analysis and microsphere model analysis. Cerebrovascular response to acetazolamide expressed by the percent increase of rCBF is estimated to be less by the microsphere model analysis than by the two-compartment model analysis. The dotted line is the line of identity.

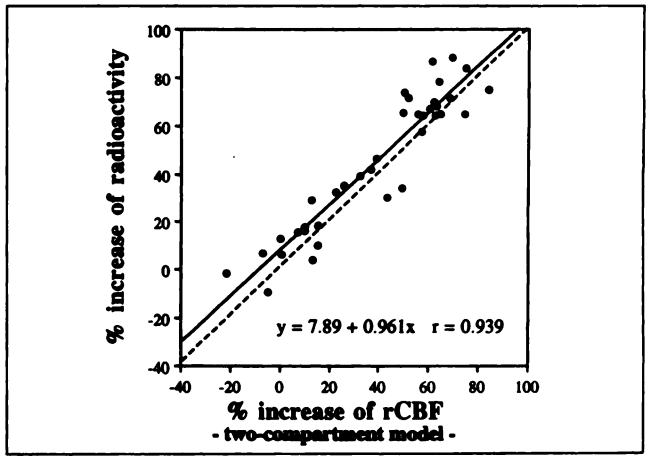

FIGURE 6. Relationship between two-compartment analysis and radioactivity change analysis. Response calculated by radioactivity change shows a good linear relationship with two-compartment model analysis. The plots show larger variation compared to Figure 5. The dotted line is the line of identity.

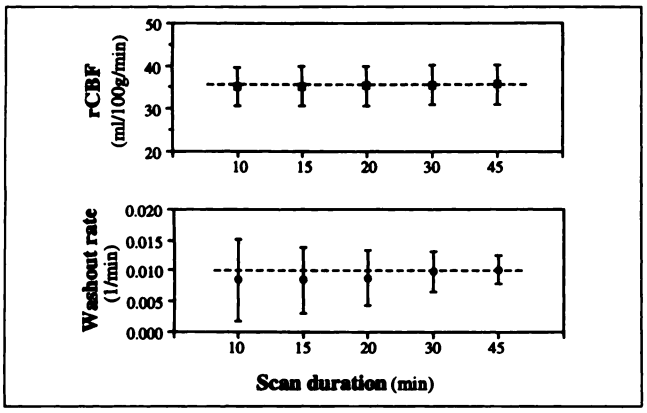

FIGURE 7. Effects of scan duration on rCBF and washout rate. The data were obtained from the dynamic SPECT for 50 min with a single dose of IMP in five patients. The rCBF on dynamic SPECT scans as short as 10 min is stable, whereas washout rate becomes unstable if the scan is shorter than 20 min.

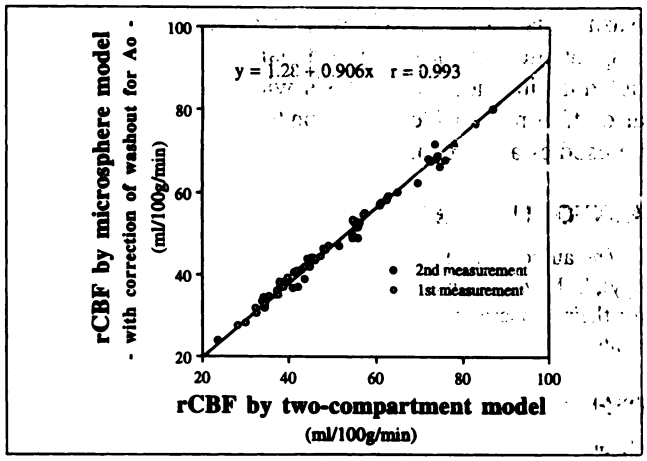

FIGURE 8. Washout correction for radioactivity from the first dose with a constant value in the microsphere model analysis. The mean value of the ratio of rCBF-to-washout rate was used as the constant value for the correction. After correction, both plots from the first and the second measurements are on the same regression line with an excellent correlation coefficient.

In the two-compartment model analysis, the effect of ACZ on the estimation of the first rCBF measurement was considered because ACZ was administered during the first measurement with a 1-min slow infusion started 13 min into the procedure. Our protocol for the reconstruction of dynamic SPECT data suggests that the last SPECT data obtained at 20 min would be affected. The estimation of rCBF, however, largely depends on the early part of the time-activity curve of the brain. The late part would affect the washout estimate (Fig. 7). The duration of data acquisition has almost no effect on rCBF for short scans of up to 10 min, whereas the washout rate may be affected for durations shorter than 20 min. In fact, for the first measurement, rCBF by the two-compartment model analysis was comparable to rCBF by the microsphere model analysis, which was calculated with the data obtained before ACZ administration and thus was not influenced by ACZ. A 3% difference between rCBF measurements by these two analyses in the patients with ACZ were the same as those in the patients without ACZ. Therefore, the rCBF estimation with two-compartment model analysis is not so sensitive to alterations of real rCBF during the later measurement, and the effect of ACZ is negligible. For the second rCBF measurement, almost maximal effect of ACZ, which is reported to be achieved 10–25 min after administration, seems to be exactly reflected on the estimated values in this study with a 60% increase from the resting values in unaffected cerebral cortices, which is comparable to those obtained by ^{133}Xe-SPECT (*7,9,11*).

For the calculation of the second rCBF with the microsphere model analysis, we applied simple subtraction of radioactivity from the first dose without considering washout because it is easier in clinical applications. Therefore, compared to two-compartment model analysis, this method showed a lower value for the second rCBF than the first, resulting in a lower value for ACZ response in both ischemic and nonischemic regions. A significant difference was seen between these regions, however, and the method seemed to be useful for identifying hemodynamically compromised brain regions. Semiquantitative analysis from the radioactivity data, compared to the two-compartment model and microsphere model analyses, showed a greater response with larger variation among patients because the input function, which differed among subjects and was larger for the second measurement dose was neglected. Discrimination between the ischemic and nonischemic regions, however, was possible with this method and is easily applicable even for a screening test.

In this study, a positive correlation was seen between rCBF and washout rate. Therefore, the ratio of rCBF-to-washout rate (or partition coefficient) was almost constant for all conditions with a mean value of 39.1 ml/g. In the previous report, we showed differences in the partition coefficient among normal and diseased regions, including noninfarcted ischemic regions (*17*). This seems to be caused by differences in the study population. Compared to the previous study, rCBF was well preserved in the ischemic regions in this study. In the microsphere model analysis, the mean value of the partition coefficient can be used to correct washout of radioactivity from the first dose. By using this constant value for all regions, microsphere model analysis yielded more precise calculation of both the second and first rCBF measurement and the response to ACZ (62.0 ± 9.3 ml/100 g/min and 52.5% ± 10.3% for nonischemic areas, and 43.3 ± 10.3 ml/100 g/min and 8.5% ± 12.9% for the ischemic areas, respectively) (Fig. 8).

CONCLUSION

The double-injection method for [^{123}I]IMP analyzed by a two-compartment model yielded good reproducibility of sequential rCBF measurement, and was sensitive enough to assess rCBF change after ACZ challenge. A simple microsphere model analysis without consideration of

washout is also a reliable way to assess cerebrovascular response despite the complex dynamics of [^{123}I]IMP. Without quantification, an analysis with radioactivity change also offers reasonable estimation to ACZ response and can be used as a screening procedure.

ACKNOWLEDGMENTS

The authors thank Drs. H. Fukuyama (Department of Neurology), S. Miyamoto and M. Tanaka (Department of Neurosurgery) for their cooperation in providing clinical information on the patients.

REFERENCES

1. Gibbs JM, Wise RJS, Leenders KL, Jones T. Evaluation of cerebral perfusion reserve in patients with carotid-artery occlusion. *Lancet* 1984;i:310–314.
2. Powers WJ, Grubb RL, Raichle ME. Physiological responses to focal cerebral ischemia in humans. *Ann Neurol* 1984;16:546–552.
3. Machac J, Vallabhajosula S. Cerebral versus myocardial stress perfusion imaging: role of pharmacological intervention in the diagnostic assessment of flow reserve. *J Nucl Med* 1994;35:41–43.
4. Ringelstein EB, Eyck SV, Mertens I. Evaluation of cerebral vasomotor reactivity by various vasodilating stimuli: comparison of CO_2 to ACZ. *J Cereb Blood Flow Metabol* 1992;12:162–168.
5. Vorstrup S, Brun B, Lassen NA. Evaluation of the cerebral vasodilatory capacity by the ACZ test before EC-IC bypass surgery in patients with occlusion of the internal carotid artery. *Stroke* 1986;17:1291–1298.
6. Kuroda S, Kamiyama H, Abe H, Houkin K, Isobe M, Mitsumori K. ACZ test in detecting reduced cerebral perfusion reserve and predicting long-term prognosis in patients with internal carotid artery occlusion. *Neurosurgery* 1993;32:912–919.
7. Sullivan HG, Kingsbury TB, Morgan ME, et al. The rCBF response to Diamox in normal subjects and cerebrovascular disease patients. *J Neurosurgery* 1987;67:525–534.
8. Bonte FJ, Devous MD, Reisch JS. The effect of ACZ on regional cerebral blood flow in normal human subjects as measured by single-photon emission computed tomography. *Invest Radiol* 1988;23:564–568.
9. Vorstrup S, Henriksen L, Paulson OB. Effect of ACZ on cerebral blood flow and cerebral metabolic rate for oxygen. *J Clin Invest* 1984;74:1634–1639.
10. Batjer HH, Devous MD, Purdy PD, et al. Improvement in regional cerebral blood flow and cerebral vasoreactivity after extracranial-intracranial arterial bypass. *Neurosurgery* 1988;22:913–919.
11. Chollet F, Celsis P, Clanet M, Guiraud-Chaumeil B, Rascol A, Marc-Vergnes JP. SPECT study of cerebral blood flow reactivity after ACZ in patients with transient ischemic attacks. *Stroke* 1989;20:458–464.
12. Burt RW, Witt RM, Cikrit D, Carter J. Increased brain retention of ^{99m}Tc-HMPAO following ACZ administration. *Clin Nucl Med* 1991;16:568–571.
13. Matsuda H, Higashi S, Kinuya K, et al. SPECT evaluation of brain perfusion reserve by the ACZ test using ^{99m}Tc-HMPAO. *Clin Nucl Med* 1991; 16:572–579.
14. Knop J, Thie A, Fuchs C, Siepmann G, Zeumer H. Technetium-99m-HMPAO-SPECT with ACZ challenge to detect hemodynamic compromise in occlusive cerebrovascular disease. *Stroke* 1992;23:1733–1742.
15. Hill TC, Hollman BL, Lovett R, et al. Initial experience with SPECT (single-photon computerized tomography) of the brain using N-isopropyl ^{123}I-p-iodoamphetamine: concise communication. *J Nucl Med* 1982;23:191–195.
16. Kuhl DE, Barrio JR, Huang SC, et al. Quantifying local cerebral blood flow by N-isopropyl-p-[^{123}I]iodoamphetamine (IMP) tomography. *J Nucl Med* 1982;23:196–203.
17. Yonekura Y, Nishizawa S, Mukai T, et al. Functional mapping of flow and back-diffusion rate of N-isopropyl-p-iodoamphetamine in human brain. *J Nucl Med* 1993;34:839–844.
18. Batjer HH, Devous MD Sr. The use of ACZ-enhanced regional cerebral blood flow measurement to predict risk to arteriovenous malformation patients. *Neurosurgery* 1992;31:213–218.
19. Grady CL, Haxby JV, Horwitz B, et al. Activation of cerebral blood flow during a visuoperceptual task in patients with Alzheimer-type dementia. *Nuerobiol Aging* 1993;14:35–44.
20. Biersack HJ, Linke D, Brassel F, et al. Technetium-99m-HMPAO brain SPECT in epileptic patients before and during unilateral hemispheric anesthesia (Wada test): report of three cases. *J Nucl Med* 1987;28:1763–1767.
21. Mathews D, Walker BS, Purdy PD, et al. Brain blood flow SPECT in temporary balloon occlusion of carotid and intracerebral arteries. *J Nucl Med* 1993;34:1239–1243.
22. Hayashida K, Hirose Y, Kaminaga T, et al. Detection of postural cerebral hypoperfusion with technetium-99m-HMPAO brain SPECT in patients with cerebrovascular disease. *J Nucl Med* 1993;34:1931–1935.
23. Murase K, Tanada S, Mogami, et al. Validity of microsphere model in cerebral blood flow measurement using N-isopropyl-p-(^{123}I) iodoamphetamine. *Med Phys* 1990;17:79–83.
24. Yokoi T, Iida H, Itoh H, Kanno I. A new graphic plot analysis for cerebral blood flow and partition coefficient with iodine-123-iodoamphetamine and dynamic SPECT validation studies using oxygen-15-water and PET. *J Nucl Med* 1993;34:498–505.
25. Nakagawara J, Takeda R, Tanaka Y, et al. Assessment of hemodynamic reserve in candidates for carotid bypass surgery using SPECT and [^{123}I]IMP activated with ACZ test. *Adv Funct Neuroimag* 1989;2:8–15.
26. Hoshi H, Ohnishi T, Jinnouchi S, et al. Cerebral blood flow study in patients with moyamoya disease evaluated by IMP SPECT. *J Nucl Med* 1994;35: 44–50.
27. Hashikawa K, Matsumoto M, Moriwaki H, et al. Sequential quantitative cerebral blood flow measurements using split dose [^{123}I]IMP SPECT method [Abstract]. *J Nucl Med* 1993;34:209P.
28. Devous MD, Stokely EM, Chehabi HH, Bonte FJ. Normal distribution of regional cerebral blood flow measured by dynamic single-photon emission tomography. *J Cereb Blood Flow Metabol* 1986;6:95–104.
29. Prohovnik I, Hakansson K, Risberg J. Observation on the functional significance of regional cerebral blood flow in "resting" normal subjects. *Neuropsychologia* 1980;18:203–217.
30. Frackowiak RJ, Lenzi GL, Jones T, Heather JD. Quantitative measurement of regional cerebral blood flow and oxygen metabolism in man using ^{15}O and positron emission tomography: theory, procedure, and normal values. *J Comput Assist Tomogr* 1980;4:727–736.