Quantification of Cerebral Blood Flow and Partition Coefficient Using Iodine-123-Iodoamphetamine

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The aim of this study was to develop a simple, noninvasive method for quantifying both regional cerebral blood flow (rCBF) and the partition coefficient (λ) using N-isopropyl-p-[^{123}I]iodoamphetamine and SPECT. **Methods:** By employing a two-compartment model (influx, K_1; outflux, k_2), a new method was introduced that requires two serial SPECT scans at 30 min and 60 min, and a single arterial sample 5 min after tracer injection. The integral of the arterial input function is inferred from the sample by using the correlation obtained from 25 subjects. Two original mathematical functions, Φ for K_1 and Γ for λ (= K_1/k_2), were obtained from the input functions of 12 subjects. The values of K_1 and λ are determined from the two scans and the single arterial sample by using these functions. The values obtained for K_1 (= rCBF) and λ were compared with those obtained by nonlinear least-squares fitting analysis and the ^{133}Xe inhalation SPECT method. **Results:** K_1 and λ were in good agreement with the values obtained by nonlinear least-squares fitting analysis ($r = 0.873$ in K_1 and $r = 0.825$ in λ), and rCBF values were closely correlated with those obtained by the ^{133}Xe method ($r = 0.843$). **Conclusion:** The proposed method has three advantages: (a) accurate, simultaneous quantification of both rCBF and the partition coefficient; (b) simplicity and noninvasiveness; and (c) a relatively short period (approximately 70 min) for the study.

Key Words: ^{123}I-iodoamphetamine; regional cerebral blood flow measurement; partition coefficient; single photon emission computed tomography; two compartment model

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Since N-isopropyl-p-[^{123}I]iodoamphetamine (IMP) crosses the blood-brain barrier and has high first-pass extraction and long retention in brain tissue (*1,2*), it has been used to map brain perfusion with SPECT. Earlier works by Kuhl et al. (*3*) sought to quantify regional cerebral blood flow (rCBF) using IMP and SPECT by applying the uptake approach based on a microsphere model. In quantifying rCBF using the microsphere model, measured values are underestimated because washout of the tracer from brain tissue is ignored (*4,5*). When SPECT data are acquired in the initial several minutes post-injection, the washout can be negligible because its value is small (*5*). However, it is difficult to obtain enough SPECT data in the period when a current head rotating camera is used. Hence, the two-compartment model (influx, K_1; outflux, k_2) has been recommended to analyze the tracer kinetics of IMP (*6–8*). To quantify rCBF by the two-compartment model with curve fitting analysis (*6,7*) or graphic analysis (*8*), both dynamic SPECT scans and serial sampling of arterial blood are required. These procedures are invasive, laborious and time consuming.

Recently, Iida et al. (*9*) reported an ideal method for quantifying rCBF using IMP based on the two-compartment model with a table look-up procedure. This method requires two SPECT scans at 40 min and 180 min post-injection and single arterial sampling. Although the procedure is simple and noninvasive, it has two disadvantages in terms of the delayed scan at 180 min. One is that precise superimposition of the region of interest (ROI) on the two SPECT images may be difficult, and the other is the length of time required for the study. In addition, a standardized input function with calibration is used instead of determining an individual input function for the particular subject, which would be ideal, but the procedure has not been adequately validated.

In this study we propose a simple, noninvasive method for quantifying both rCBF and the partition coefficient with IMP and SPECT based on the two-compartment model. Two serial SPECT scans in the early phase without the delayed SPECT scan and one-point sampling of arterial blood are required, resulting in a precise superimposition of the ROIs and a relatively short period of approximately 70 min for the study. Although this method is based on the two-compartment model, as used in the table look-up method (*9*), the mathematical functions are originated by a new theoretical approach. In addition, the one-point sampling method (*10*) was used, which did not require the standardized input function with calibration as used in the table look-up method. To validate the method, the values of rCBF and the partition coefficient were compared with those obtained by two other independent techniques, nonlinear least-squares fitting (NLLSF) analysis and ^{133}Xe inhalation SPECT.

MATERIALS AND METHODS

Theory

Iodine-123-IMP is assumed to be freely diffusible from the blood pool to brain tissue. To analyze its kinetics in the brain, the two-compartment model was employed in this study as described in previous reports (*6,8,9*). Although the physiological kinetics have not been clarified, the model was empirically validated to use in describing the IMP kinetics (*9*). The following first-order differential equation can be proposed:

$$\frac{dCb(t)}{dt} = K_1Ca(t) - k_2Cb(t), \qquad \text{Eq. 1}$$

where Ca(t) and Cb(t) are the respective concentrations of ^{123}I-IMP in arterial blood (μCi/ml) and brain tissue (μCi/g) corrected for physical decay. K_1 is the influx rate constant of the tracer across the blood-brain barrier, and k_2 is the outflux rate constant (per minute) for washout of IMP from the brain. Since the first-pass extraction fraction of IMP is very high (assumed to be 1.0), K_1 can be identified as rCBF in milliliters per gram per minute. The brain tissue-blood partition coefficient of IMP, λ (ml/g), is defined as follows:

$$\lambda = \frac{K_1}{k_2}. \qquad \text{Eq. 2}$$

When Equation 1 is solved for K_1, the following formula is obtained:

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$$K_1 = \frac{Cb(t) + k_2 \int_0^t Cb(s)\,ds}{\int_0^t Ca(s)\,ds}. \quad \text{Eq. 3}$$

If time t is determined at 5 min, and Cb(30 min) is applied, Equation 3 is transformed as follows:

$$K_1 = \frac{Cb(5\text{ min}) + k_2 \int_0^{5\text{ min}} Cb(s)\,ds}{\int_0^{5\text{ min}} Ca(s)\,ds}$$

$$= \frac{Cb(30\text{ min})}{\int_0^{5\text{ min}} Ca(t)\,dt} \times \frac{Cb(5\text{ min}) + k_2 \int_0^{5\text{ min}} Cb(t)\,dt}{Cb(30\text{ min})}. \quad \text{Eq. 4}$$

On the other hand, when Equation 1 is solved for Cb(t), the following formula is obtained:

$$Cb(t) = K_1 \int_0^t Ca(x) \exp[-k_2(t-x)]\,dx. \quad \text{Eq. 5}$$

When input function Ca(t) is determined, a relationship between the ratio of $Cb(t_1)/Cb(t_2)$ and value of k_2 is computed (*9*), in which t_1 and t_2 are arbitrary. By using the relationship between $Cb(t_1 = T_1)/Cb(t_2 = T_2)$ and k_2 calculated from Ca(t) beforehand, k_2 is obtained from $Cb(T_1)/Cb(T_2)$. With k_2, the values of $Cb(t_1)/Cb(t_2)$ for various t_1 and t_2 can be determined from Ca(t), and then the relative values of Cb(t) are obtained. That is, k_2 and the relative value of Cb(t) are computed from $Cb(T_1)/Cb(T_2)$ by using Ca(t). The second part of the fraction on the right of Equation 4 is computed from k_2 and the relative value of Cb(t), i.e., from $Cb(T_1)/Cb(T_2)$. In this study, T_1 and T_2 are set at 30 min and 60 min, respectively, and the second part of the fraction on the right of Equation 4 is substituted for the following function Φ in Cb(30 min)/Cb(60 min) variables:

$$\Phi\left\{\frac{Cb(30\text{ min})}{Cb(60\text{ min})}\right\} = \frac{Cb(5\text{ min}) + k_2 \int_0^{5\text{ min}} Cb(t)\,dt}{Cb(30\text{ min})}. \quad \text{Eq. 6}$$

Then Equation 4 is represented as follows:

$$K_1 = \frac{Cb(30\text{ min})}{\int_0^{5\text{ min}} Ca(t)\,dt} \times \Phi\left\{\frac{Cb(30\text{ min})}{Cb(60\text{ min})}\right\}. \quad \text{Eq. 7}$$

In a brief summary, K_1 is calculated from $\int_0^{5\text{ min}} Ca(t)dt$ and two SPECT scans at 30 min and 60 min using the function Φ that is computed from Ca(t) based on the two-compartment model.

In the same way mentioned above, λ is described as follows:

$$\lambda = \frac{Cb(30\text{ min})}{\int_0^{5\text{ min}} Ca(t)\,dt} \times \frac{Cb(5\text{ min}) + k_2 \int_0^{5\text{ min}} Cb(t)\,dt}{k_2 Cb(30\text{ min})}$$

$$= \frac{Cb(30\text{ min})}{\int_0^{5\text{ min}} Ca(t)\,dt} \times \Gamma\left\{\frac{Cb(30\text{ min})}{Cb(60\text{ min})}\right\}. \quad \text{Eq. 8}$$

When the functions Φ and Γ in Equations 7 and 8 are prepared beforehand by averaging the individual functions computed from Ca(t) of several subjects, values of the functions are calculated by two SPECT scans without any data of Ca(t). In addition, when $\int_0^{5\text{ min}} Ca(t)dt$ in Equations 7 and 8 is obtained from a single sample of arterial blood by using the one-point sampling method (*10*) mentioned below, K_1 and λ are determined by two serial SPECT scans with single arterial sampling.

Subjects

The subjects of this study consisted of three groups. Informed consent was obtained from each subject. None of the subjects had heart or pulmonary disease.

Group 1. To obtain the functions Φ and Γ, 12 subjects between the ages of 18 and 74 yr (6 men and 6 women; age 48.0 ± 18.9 yr) were examined by serial arterial sampling. These subjects included 10 patients with various neurological diseases and 2 normal control subjects who were smokers. Two patients had chronic cerebral infarction, two had arteriovenous malformation and one each had Moya-Moya disease, migraine, epilepsy, amyotrophic lateral sclerosis, Pick disease and Parkinson's disease.

Group 2. Twenty-five subjects between the ages of 15 and 73 yr (18 men and 7 women; age 45.9 ± 23.6 yr) were examined to obtain $\int_0^{5\text{ min}} Ca(t)dt$ for the one-point sampling method. The subjects consisted of 12 patients with cerebrovascular disease, 6 with degenerative disease, 4 with epilepsy and 3 normal control subjects including 2 smokers.

Group 3. To validate values of rCBF and λ obtained by the present method, the 12 subjects listed in Table 1 were examined by the following SPECT studies. Eight subjects underwent dynamic SPECT scans in which two patients also underwent ^{133}Xe inhalation SPECT studies. The other four subjects, all normal control subjects including two smokers, underwent two serial SPECT scans for the present method and ^{133}Xe inhalation SPECT studies for validation.

Preparation of Functions Φ and Γ

The input function Ca(t) of each of the subjects described in Group 1 was individually measured by sequential arterial sampling. A dose of 222 MBq of IMP (Nihon Medi-Physics, Takarazuka, Japan) was injected via a cubital vein during 1 min, and arterial blood was simultaneously withdrawn through a catheter inserted into the radial artery of the opposite side. Blood was withdrawn every 15 sec from 0 to 2 min, every 30 sec from 2 to 5 min, every minute from 5 to 10 min and 12, 14, 16, 20, 25, 30, 40, 50 and 60 min after IMP injection. The fraction of true tracer activity in each arterial blood sample (= N) was examined by the octanol extraction method (*3*). Ca(t) is the product of activity in a blood sample obtained at time t and the value of N (*6–9*). Discrete values of individual functions Φ and Γ in Equations 6 and 8 were computed using individual Ca(t) of 12 subjects then, averaging these values,

TABLE 1
Patient Profiles and SPECT Studies

Patient no.	Sex	Age (yr)	Clinical diagnosis	Validation SPECT studies
1	M	56	Cerebral infarction	Dynamic SPECT and ^{133}Xe SPECT
2	M	73	Cerebral infarction	Dynamic SPECT and ^{133}Xe SPECT
3	M	66	ALS	Dynamic SPECT
4	M	67	Pick disease	Dynamic SPECT
5	M	74	Parkinson's disease (grade 2)	Dynamic SPECT
6	F	55	Parkinson's disease (grade 3)	Dynamic SPECT Dynamic SPECT (n = 2)
7–12 (total 6)	all M	35.7 ± 15.2	Normal control subjects	Two serial SPECT and ^{133}Xe SPECT (n = 4)
Age (mean ± s.d.)		50.4 ± 19.3		

ALS = amyotrophic lateral sclerosis; grade = severity of Parkinson's disease classified by Hoehn and Yahr (*13*).

we obtained the mean indiscrete values of functions Φ and Γ and their s.d. interpolated by polynomial approximation (Fig. 1).

One-Point Sampling Method

To obtain $\int_0^{5\,min}$ Ca(t)dt in Equations 7 and 8 from a single arterial sample, the one-point sampling method previously reported (*10*) was introduced instead of the continuous withdrawal or sequential sampling of arterial blood. The integral of Ca(t) from 0 to 5 min is estimated by using a regression line from a single arterial sample without octanol treatment (*10*). In this study, we further advanced the method by examining more subjects as described in Group 2. After the injection of IMP, the continuous withdrawal of arterial blood was carried out from 0 to 5 min, after which a single arterial sample was withdrawn at 5, 6, 7, 8, 9 and 10 min. The fraction of true tracer activity in the continuously withdrawn blood sample (= N′) was examined by the octanol extraction method (*3*). $\int_0^{5\,min}$ Ca(t)dt is the product of activity in the continuously withdrawn sample and the value of N′. The relation between $\int_0^{5\,min}$ Ca(t)dt and the activity in each single sample without octanol treatment was examined. Then the optimum time for single sampling was determined as the time when the best correlation was obtained. In addition, we estimated the error resulting from the deviation of the optimum sampling time to correct the activity in a single sample when sampling was delayed for some reason.

SPECT Data Acquisition

After IMP was injected intravenously in the subjects in Group 3, dynamic SPECT studies were performed on eight subjects in Table 1 using a ring-type SPECT scanner, Headtome SET-050 (Shimadzu, Kyoto, Japan), equipped with a high-resolution collimator. Dynamic scans were performed at a scan duration of 5 min from 5 (mid-scan time) to 65 min post-injection. To calculate Cb(30 min)/Cb(60 min) in the present method, the SPECT data obtained at 30 min and 60 min were used. SPECT data were acquired with 20 simultaneous slices at 5-mm intervals. Images were reconstructed in 128 × 128 matrices using a filtered back-projection algorithm with a RAMP and Butterworth filter. The effective spatial resolution was 8.7 mm in full width at half maximum at the center of the transaxial field of view. Attenuation correction was done numerically by assuming an elliptical brain outline (*11*).

Two serial SPECT scans were performed on four normal control subjects with the same SPECT scanner. SPECT data were acquired at 30 min (mid-scan time) and 60 min, each with a 20-min scan duration; these were then used to calculate Cb(30 min)/Cb(60 min). The procedures used for image reconstruction and other procedures were the same as mentioned above.

Cross Calibration

Cross-calibration was performed using a series of uniform cylindrical phantoms (16 cm inner diameter × 15 cm height) composed of water with 1 of 11 concentrations of IMP. The activity of the SPECT images on the computer was linearly related to the activity concentration in the phantom measured with the well-scintillation counter.

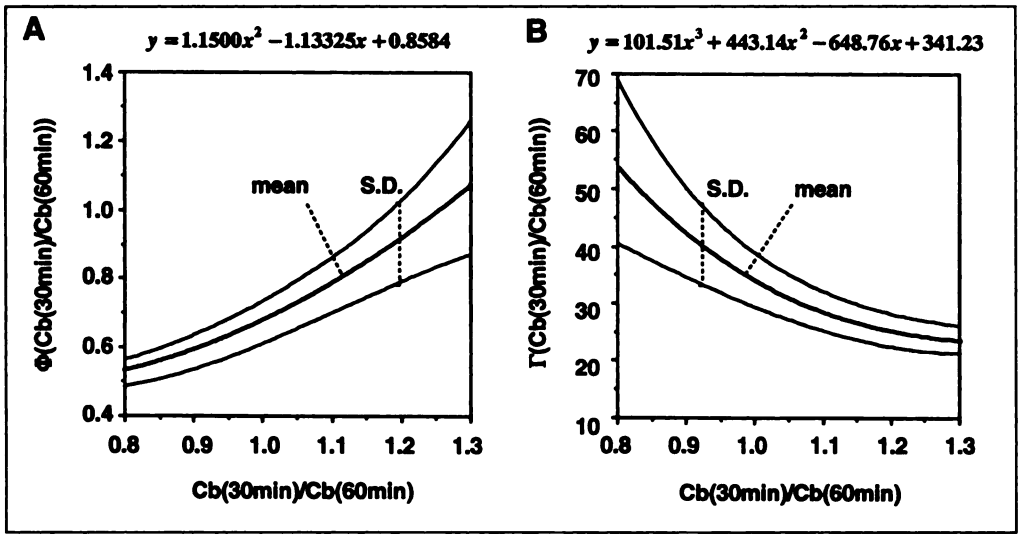

FIGURE 1. The mathematical functions Φ (A) and Γ (B) in Cb(30 min)/Cb(60 min) variables, obtained by averaging those calculated from arterial input functions of 12 subjects based on the two-compartment model. The bold and fine lines show means ± s.d., respectively.

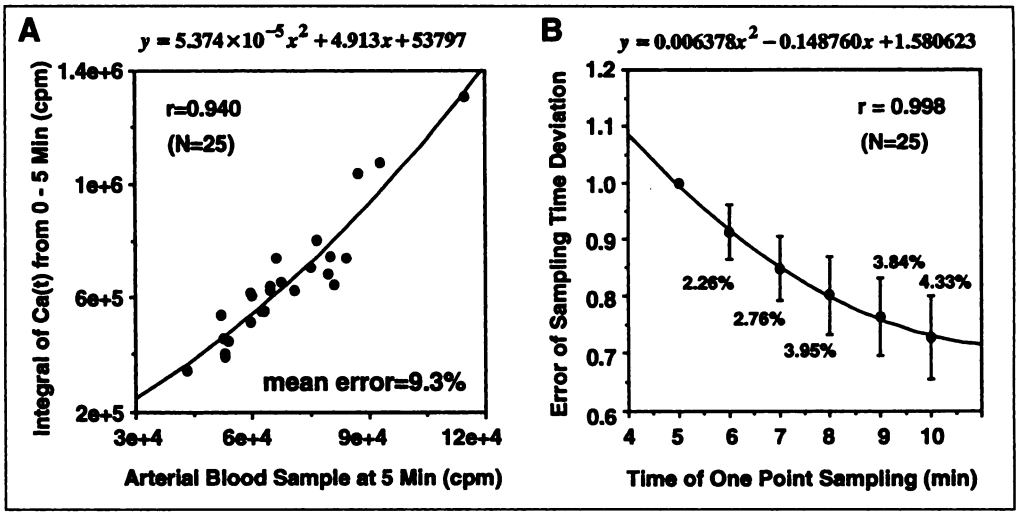

FIGURE 2. (A) Correlation between one arterial sample taken at 5 min and the integral of Ca(t) obtained by the continuous arterial withdrawal from 0 to 5 min. (B) An error resulting from the deviation of sampling time. The ordinate represents the ratio of activity of each sample obtained at 6–10 min to that at 5 min. The activity of the sample can be corrected to that at 5 min by dividing by the value obtained from the regression line. The percentage error of the correction at each time point is shown.

Validation by NLLSF Analysis

In the dynamic SPECT studies, sequential arterial sampling was performed following tracer injection using the same procedure described in *Preparation of Functions* Φ *and* Γ. The parameters K_1, k_2 and λ were obtained by NLLSF analysis according to the two-compartment model (*6–8*). The values of K_1 and λ obtained by the present method were compared with those obtained by NLLSF analysis. When measuring K_1 and λ, irregular shaped ROIs were placed in the cerebellum, brain stem, cerebral cortices and centrum semiovale (30 ROIs in each subject) on the transaxial slice computer images.

Validation by ^{133}Xe Inhalation SPECT

Approximately 60 min before the IMP SPECT studies, ^{133}Xe inhalation SPECT studies were performed on six subjects in Group 3 (Table 1). SPECT data were acquired with the same SPECT scanner equipped with a high-sensitivity collimator. rCBF was measured by the sequential picture method (*12*), with similar irregularly shaped ROIs placed in the brain except for the brain stem. Since rCBF is affected by $PaCO_2$, the rCBF values obtained were corrected by the factor of 1.03 ml/min for alterations of 1 mmHg in arterial carbon dioxide tension on ^{133}Xe studies in comparison with following IMP studies (*6*).

RESULTS

Functions Φ and Γ

Figure 1 shows the means and s.d. of functions Φ and Γ, which were obtained by averaging the individual functions of the 12 subjects. By using the mean functions, Φ[Cb(30 min)/Cb(60 min)] and Γ[Cb(30 min)/Cb(60 min)], values of a patient can be determined from two SPECT scans without obtaining fresh individual input functions. Errors in determining the values are considered to depend on variations of the functions in Figure 1. When K_1 ranged from 0.3 to 0.7 ml/g/min and λ from 15 to 35 ml/g, in which Cb(30 min)/Cb(60 min) ranged from 0.83 to 1.29, the mean coefficient of variance (= s.d./mean value), which indicates statistical variations in the functions, was approximately 10.5% for Φ and 14.5% for Γ. There were no age- and gender-dependencies in these functions.

One-Point Sampling Method

Examining the relationship between $\int_0^{5\ min}$ Ca(s)ds and the activity in each single sample obtained from 5 to 10 min, we found that the best correlation (r = 0.940) was obtained at 5 min (Fig. 2A). By using the regression line, $\int_0^{5\ min}$ Ca(s)ds can be inferred by a single sample obtained at 5 min with a mean error of approximately 9.3%. The data of mean percent error were examined on age by classifying into three groups: A, ≈19 yr (4 subjects); B, 20 ≈ 59 yr (11 subjects); and C, ≈60 yr (10 subjects), and on sex. Mean ± s.d. of the percent error was 12.0 ± 10.1% in Group A, 9.8 ± 5.6% in Group B and 7.2 ± 4.7% in the Group C, and 7.1 ± 5.9% in the man and 10.8 ± 6.0% in the woman, respectively. There were no statistically significant differences among the groups, and between the man and woman.

The ratios of activity of each single sample obtained from 5 to 10 min and that obtained at 5 min were calculated (Fig. 2B). If sampling is delayed beyond 5 min, the activity in the sample can be corrected to that at 5 min by dividing by the value obtained from the regression line in Figure 2B. The error of correction was 2.26% at 6 min, 2.76% at 7 min, 3.95% at 8 min, 3.84% at 9 min and 4.33% at 10 min.

Comparisons of K_1 and λ

Figure 3 compares K_1 and λ obtained by the present method with the values calculated by NLLSF analysis. They show good agreement (r = 0.873 for K_1 and 0.825 for λ). The mean percentage error was 8.9% for K_1 and 10.0% for λ. Each regression line was near to y = x. Figure 4 shows a comparison of K_1 obtained by the present method and ^{133}Xe inhalation SPECT. We observed a good correlation between the two studies (r = 0.843) with a mean error of 13.2%.

DISCUSSION

We proposed a simple, noninvasive method for quantifying both rCBF and the partition coefficient based on the two-compartment model. The method has three advantages: (a) accurate, simultaneous quantification of rCBF and the partition coefficient using simplified calculations based on the two-compartment model; (b) simplicity and noninvasiveness supported by one-point arterial sampling without octanol treatment; and (c) two serial SPECT scans in the early phase, eliminating the need for a delayed scan.

The values of rCBF and λ were in good agreement with those obtained by other independent techniques, NLLSF analysis and ^{133}Xe inhalation SPECT, indicating the validity of the present method. The procedures, including two serial SPECT scans and the one-point sampling method, are simple and noninvasive. With two SPECT scans at 30 min and 60 min post-injection, patients are strapped to the scanning bed for approximately 50 min (20 min for each scan with a 10-min interval), an amount of time that may be more tolerable for patients. These scans can be obtained with a current head rotating camera. Laborious procedures to achieve precise positioning for delayed scans are

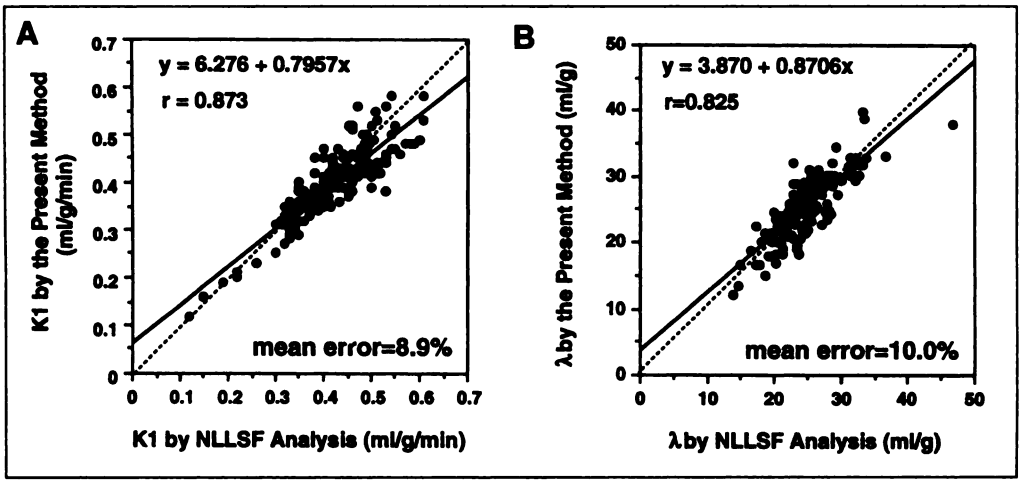

FIGURE 3. Correlations between the values of K_1 (A) and λ (B) obtained by the present method and by NLLSF analysis based on the two-compartment model. The mean percent error estimated by the present method was approximately 8.9% in K_1 and 10.0% in λ. The broken line shows the line of identity.

not required because of the two serial SPECT scans. Therefore, precise superimposition of ROIs on the two SPECT images is possible. Data on arterial blood are obtained by the one-point sampling method, which is simple and relatively accurate. A method of correcting the data when sampling is delayed was also proposed. Therefore, the present method is both useful and readily available in most institutions.

Accuracy of Measured Values

The accuracy of the measured values of K_1 and λ depends on statistical variations in the functions Φ and Γ (Fig. 1) and the one-point sampling method (Fig. 2). When K_1 and λ ranged from 0.3 to 0.7 ml/g/min and 15 to 35 ml/g in the two-compartment model, the mean statistical variation of the functions Φ and Γ was 10.5% and 14.5%, respectively. The mean percent error in the one-point sampling method was 9.3%. Hence the statistical errors of K_1 and λ obtained by the present method are estimated at $\sqrt{10.5^2 + 9.3^2} = 14.0\%$ and $\sqrt{14.5^2 + 9.3^2} = 17.2\%$, respectively. These errors are not small, because as Cb(30 min)/Cb(60 min) increases (high K_1 and low λ), the error in K_1 increases (Fig. 1A), and as Cb(30 min)/Cb(60 min) decreases (low K_1 and high λ), the error in λ increases (Fig. 1B). Except for these situations, the statistical errors are not large, and values obtained are considered to be accurate. Indeed, in the comparative study, the values were well correlated with those of other independent techniques, and the mean percent errors of K_1 (8.9% in NLLSF and 13.2% in ^{133}Xe SPECT) and λ (10.0%) are allowable in clinical studies.

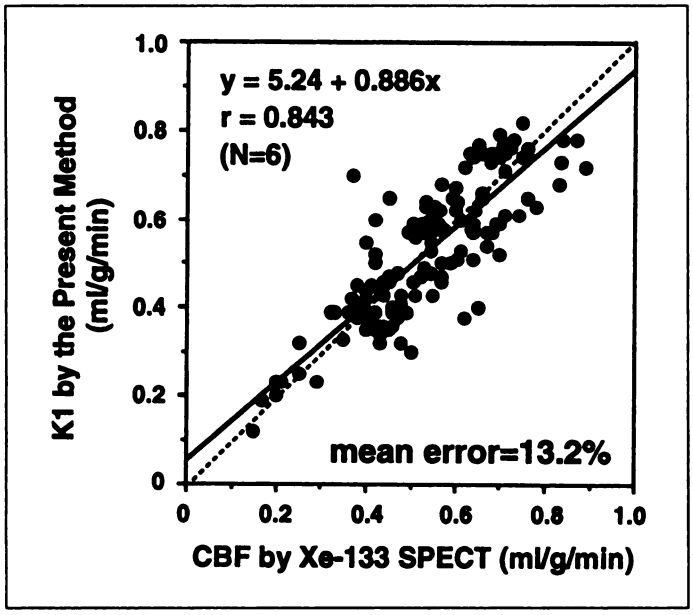

FIGURE 4. Correlations between the values of K_1 obtained by the present method and by ^{133}Xe inhalation SPECT. The values were in good agreement, and the mean percent error was approximately 10.9%. The broken line shows the line of identity.

Limitations

Since the proposed functions Φ and Γ in Figure 1 and one-point sampling method in Figure 2 were obtained by examining subjects who had no heart or pulmonary disease, study needs to be carried out in patients with those diseases. There were no age- and gender-dependencies in the functions Φ and Γ in this study with 12 subjects. However, further study with a large number of the subjects will be required.

Although the times of the two serial SPECT scans were set at 30 min and 60 min in this study, we did not examine which time combination of scans was best. When a current head rotating camera is used with a relatively long scan duration, it is not recommended that the first scan be performed too soon after injection, because tracer activity has not yet reached a plateau and is still increasing in brain tissue. In addition, to avoid prolonged SPECT studies and several laborious procedures, the second scan can not be too late. Hence the proposed time combination may be appropriate.

CONCLUSION

The proposed method is able to provide accurate, simultaneous quantification of rCBF and λ by a simple, non-invasive procedure supported by a single arterial sampling and two serial SPECT scans with a relatively short period. The method is useful in routine clinical SPECT studies.

REFERENCES

1. Winchell HS, Baldwin RM, Lin TH. Development of I-123-labeled amines for brain studies: localization of I-123 iodophenylalkyl amines in rat brain. *J Nucl Med* 1980;21:940–946.
2. Winchell HS, Horst WD, Braun L, Oldendorf WH, Hatner R, Parker H. N-isopropyl-[^{123}I] *p*-iodoamphetamine: single-pass uptake and washout; binding to brain synaptosomes; and localization in dog and monkey brain. *J Nucl Med* 1980;21:947–952.
3. 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.
4. Murase K, Tanada S, Mogami H, et al. Validity of microsphere model in cerebral blood flow measurement using N-isopropyl-p-(I-123) iodoamphetamine. *Med Phys* 1990;17: 79–83.
5. Ohkubo M, Odano I, Takahashi N, Sakai K. Can the microsphere model be applied to cerebral blood flow measurement using N-isopropyl-p-[^{123}I] iodoamphetamine with SPECT regardless of washout from brain tissue? *Nucl Med Commun* 1995;16:1026–1033.
6. Greenberg JH, Kushner M, Rango M, et al. Validation studies of iodine-123-

iodoamphetamine as a cerebral blood flow tracer using emission tomography. *J Nucl Med* 1990;31:1364–1369.
7. Yonekura Y, Nishizawa S, Mukai T, et al. Functional mapping of flow and back-diffusion rate of N-isopropyl-iodoamphetamine in human brain. *J Nucl Med* 1993;34:839–844.
8. 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.
9. Iida H, Itoh H, Bloomfield PM, et al. A method to quantitate cerebral blood flow using a rotating gamma camera and iodine-123 iodoamphetamine with one blood sampling. *Eur J Nucl Med* 1994;21:1072–1084.
10. Odano I, Ohkubo M, Takahashi N, Higuchi T. A new method of regional cerebral blood flow measurement using one-point arterial sampling based on the microsphere model with N-isopropyl-p-[^{123}I]-iodoamphetamine SPECT. *Nucl Med Commun* 1994;15:560–564.
11. Kanno I, Uemura K, Miura S, Miura Y. HEADTOME: a hybrid emission tomograph for single photon and positron emission imaging of the brain. *J Comput Assisted Tomogr* 1981;5:216–226.
12. Kanno I, Lassen NA. Two methods for calculating regional cerebral blood flow from emission computed tomography of inert gas concentrations. *J Comput Assisted Tomogr* 1979;3:71–76.
13. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology* 1967;17:427–442.

Regional Differences in Technetium-99m-ECD Clearance on Brain SPECT in Healthy Subjects

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The aim of this study was to evaluate the in vivo stability of ECD brain SPECT. **Methods:** Twenty normal volunteers (35.4 ± 9.1 yr) each had six ECD scans at 30, 60, 120, 240, 360 and 480 min postinjection. Each scan was acquired for 24 min using a triple-head SPECT system. Average counts per pixel were measured from frontal, temporal, parietal, occipital, cerebellum, basal ganglia, thalamus and white matter regions. ECD clearance rates were calculated by fitting regional time activity data to a monoexponential equation. Regional gray-to-white matter (G/W) and gray-to-cerebellum (G/C) ratios were calculated for each scan. Analysis of variance was used to compare regional ECD clearance and ratio measurements. **Results:** The average ECD clearance was 4.3%/hr. There was a significant regional variation in the ECD clearance, being higher for occipital (6.34%/hr) but lower for both white matter (2.39%/hr) and thalamus (2.45%/hr). Both G/W and G/C ratios showed a significant regional variation with time. The overall G/W ratio was 2.13 at 30 min and became progressively lower after 2 hr, reaching 1.78 at 8 hr. All regional G/W ratios declined with time except for thalamus where it remained constant at 2.15. The overall G/C ratio was 0.984 at 30 min but it declined after 4 hr, reaching 0.955 at 8 hr. All regional G/C ratios declined with time except for thalamus where it increased progressively from 0.955 to 1.120 at 8 hr. **Conclusion:** ECD clears from normal brain slowly and shows a significant regional variation. As a result, G/W contrast begins to decrease after 2 hr and the gray-matter activity pattern becomes significantly different after 4 hr. Therefore, the optimal imaging time may be between 30–120 min. However, images obtained up to 4 hr still maintain the initial gray-matter activity pattern.

Key Words: technetium-99m-ethyl cysteinate dimer; brain SPECT; regional cerebral blood flow

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Technetium-99m-ethyl cysteinate dimer (ECD) is a relatively new ^{99m}Tc-labeled lipophilic tracer that became available clinically for SPECT imaging of regional cerebral blood flow (rCBF) (*1*). The clinical usefulness of ECD brain SPECT has been recently evaluated in several neurological conditions including cerebrovascular disease (*2–6*), dementia (*7*) and epilepsy (*8–10*). Compared with the previously introduced ^{99m}Tc-HMPAO, ECD has a faster blood clearance providing more favorable radiation dosimetry and a higher signal-to-noise ratio (*1*) and is chemically stable in vitro for several hours after reconstitution (*11*). In contrast, HMPAO must be used within 30 min after reconstitution because the labeled compound rapidly decomposes in vitro (*12*) although a more stable formulation has been recently introduced. The purpose of this study was to evaluate another important property of ECD relevant to SPECT imaging, namely, its in vivo stability in the brain.

On intravenous injection, ECD like HMPAO crosses the blood brain barrier and becomes rapidly trapped in the brain in proportion to rCBF. The retention of the tracer in the brain is related to de-esterification to polar complex(es) for ECD (*13*) whereas it is linked to the reaction with glutathione for HMPAO (*14*). Several ECD imaging studies in normal subjects and patients showed that ECD clears slowly from the brain without any significant regional variations, i.e., equally from all regions of the brain including the white matter (*11,15–18*). The lack of differential elimination of ECD from the brain suggests that SPECT images obtained several hours postinjection can still reflect the initial activity pattern. However, there have also been a few studies suggesting that there may be some regional variation in ECD clearance (*19–21*).

The in vivo stability of tracer distribution may become a crucial issue in certain situations where SPECT imaging cannot be performed for several hours postinjection. For example, in epilepsy a significant delay in imaging may be necessary after ictal tracer injection because patients might be transferred from the EEG-monitoring unit to the imaging department or the camera might be busy with other patients (*8*). A similar situation may arise for patients with acute ischemic stroke where earliest rCBF measurements are desired but emergency treatment measures may preclude immediate scanning (*22*). Previously, we evaluated the feasibility of rCBF imaging of subjects in different stages of sleep by administering ECD at night during sleep and performing SPECT imaging conveniently in the morning when subjects awaken (*23*). To closely examine the issue of in vivo stability of ECD, we evaluated the

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