Acta Medica et Biologica
Vol. 43, No. 3, 165-171, 1995

Quantitative Assessment of Cerebral Blood Flow Measurement Using the Microsphere Model with N-isopropyl-p-[^{123}I] iodoamphetamine SPECT: Simulation Analysis for the Influence of Washout from Brain Tissue

Masaki OHKUBO[1], Ikuo ODANO[2], Naoya TAKAHASHI[2] and Kunio SAKAI[2]

[1]Department of Radiological Technology, College of Biomedical Technology, Niigata University and [2]Department of Radiology, Niigata University School of Medicine, Niigata, Japan

Received April 14 1995; accepted May 16 1995

Summary. **The microsphere model and the continuous withdrawal of arterial blood have been commonly used in clinical studies when measuring regional cerebral blood flow (rCBF) by N-isopropyl-p-[^{123}I]iodoamphetamine (IMP) SPECT. The method is considered to underestimate rCBF because of the washout of the tracer from brain tissue with increasing time after injection; however, the extent of this underestimation is not known. To assess whether this underestimation can be quantitatively determined and until how long after injection the microsphere model can be applied to obtain accurate measurements of rCBF, we performed a simulation analysis. Simulation was based on the microsphere model and the 2-compartment model using the standard time-activity course of ^{123}I-IMP in arterial blood (standard input function), the accuracy of which could be validated. The values of rCBF calculated by the microsphere method following the injection of ^{123}I-IMP were compared with those given in the 2-compartment model [influx; K_1(rCBF) and outflux; k_2 (washout)]. As results, with the microsphere method, rCBF values became lower with the time after injection. The rate of underestimation of rCBF was determined to be 4.6% at 5 min, 10.2% at 10 min and 15.1% at 15 min. Since 4.6% is considered negligible in clinical studies, we concluded that the microsphere model could be applied to obtain accurate measurements of rCBF up to approximately 5 min, regardless of washout. The results of this simulation were confirmed clinically in 11 patients with various cerebral diseases.**

Key words—rCBF measurement, SPECT, ^{123}I-IMP, microsphere model, tracer kinetics.

Correspondence: Masaki Ohkubo, Department of Radiological Technology, College of Biomedical Technology, Niigata University, Asahimachi 2-746, Niigata 951, Japan.

INTRODUCTION

N-isopropyl-p-[^{123}I]iodoamphetamine (^{123}I-IMP)[1,2] has been used as a tracer for cerebral perfusion with single photon emission computed tomography (SPECT). As it has the advantages of high first-pass extraction and subsequent retention in the brain, there have been many reports on the quantitative measurement of regional cerebral blood flow (rCBF).[3-11] Among these studies, the method based on the microsphere model with the continuous withdrawal of arterial blood (microsphere method) reported by Kuhl et al.[3] has been considered to be accurate, and the values of rCBF have shown good agreement with those obtained by the ^{133}Xe three-dimensional method[4] and the ^{15}O-water positron emission tomography (PET) method.[5] On the other hand, several studies have indicated the influence of ^{123}I-IMP washout from brain tissue,[5,12,13] and shown that the microsphere method underestimated rCBF with increasing scan duration of SPECT, indicating that early scanning was required.[6-8] These studies on the underestimation of rCBF, however, were based on clinical SPECT data, and were considered to include various errors amd influences other than washout. Quantitative assessment of the underestimation has not been adequate, and it is not known until when the microsphere model can be applied to obtain accurate measurements of rCBF.

In this study, we assessed quantitatively the underestimation of rCBF by the microsphere method as a result of washout, and determined the time limit for applying the microsphere model to obtain accurate

rCBF measurements. Quantitative assessment was tried by a simulation analysis based on the microsphere model and the 2-compartment model using the standard time-activity course of ^{123}I-IMP in arterial blood (standard input function). For the accuracy of this simulation, the standard input function was validated. The results were also investigated by comparing rCBF measurement by the microsphere method with that by the ^{133}Xe inhalation method, both of which were used in 11 patients with various cerebral diseases.

MATERIALS AND METHODS

Theory

When the kinetics of ^{123}I-IMP in the brain are assumed to be analyzed with the 2-compartment model,[6-8,14] the following equation can be proposed:[15]

$$\frac{dC_b(t)}{dt}=K_1C_a(t)-k_2C_b(t) \qquad (1)$$

where Cb(t) and Ca(t) are the decay-corrected radioactivity concentration of ^{123}I-IMP in brain tissue (μCi/g) and arterial blood (μCi/ml), respectively. The value of Cb(t) is clinically derived from SPECT data, and t is the mid-scan time of SPECT. K_1 is the influx rate constant of the tracer across the blood-brain barrier, and k_2 is the outflux rate constant (/min) for the washout of ^{123}I-IMP from brain tissue. Since the extraction of ^{123}I-IMP is very high,[1,3] K_1 is identified as rCBF (ml/g/min). When the brain tissue-blood partition coefficient is $\lambda=K_1/k_2$(ml/g) and the tissue fraction is α, the product of the partition coefficient and the tissue fraction is distribution volume (V_d).[14,16,17] If the partial volume effect of a region of interest is sufficiently small or negligible, then α equals 1, and the distribution volume is identified as the partition coefficient and defined as K_1/k_2.

The integration of Equation (1) gives the following equation for K_1:

$$K_1=\frac{C_b(t)+k_2\int_0^t C_b(s)ds}{\int_0^t C_a(s)ds} \qquad (2)$$

K_1 calculated from Equation (2) is identified as rCBF in the 2-compartment model.

In the microsphere model, the approximation:

$$C_b(t) \gg k_2\int_0^t C_b(s)ds \qquad (3)$$

is assumed for the numerator in Equation (2) because $k_2 \ll 1$.[6-8] By using the approximation in Equation (3), Equation (2) can be transformed as:

$$K_1=\frac{C_b(t)}{\int_0^t C_a(s)ds} \qquad (4)$$

K_1 calculated from Equation (4) is identified as rCBF in the microsphere model. In the early phase after ^{123}I-IMP injection, as the integral term $\int_0^t C_b(s)ds$ in Equation (3) is not much larger than the left term of $C_b(t)$, the approximation in Equation (3) is applicable, and K_1 can be accurately calculated from Equation (4). However, in the late phase, as the term $\int_0^t C_b(s)ds$ in Equation (3) increases, the approximation is not applicable even at $k_2 \ll 1$. K_1 is, therefore, calculated as being lower by Equation (4) than by Equation (2), due to the omission of $k_2\int_0^t C_b(s)ds$. Thus, as time t increases, the microsphere method underestimates K_1 in comparison with the 2-compartment model. Also, with the increase in $k_2(=K_1/V_d)$, that is, the increase is K_1 and/or the decrease in V_d, K_1 is calculated to be lower because of the invalid approximation in Equation (3).

Standard input function

To evaluate the underestimation of rCBF by the microsphere method, a simulation analysis was performed. This simulation required the relative time-activity courses of ^{123}I-IMP in arterial blood, that is, the relative pattern of Ca(t) defined in Equation (1). We prepared the "standard input function" as its pattern, which was similar to the averaged and normalized time-course of relative ^{123}I-IMP activity previously reported by Iida et al.[14,18] We obtained the standard input function by averaging the time-activity courses of arterial blood withdrawn by multiple serial sampling from 10 subjects. The subjects, seven patients with cerebrovascular diseases and three normal controls, were non-smokers and had no heart or pulmonary disease. A dose of 222 MBq of ^{123}I-IMP (Nihon Medi-Physics, Takarazuka, Japan) was injected via a cubital vein during 1 min, and intermittent arterial blood sampling was simultaneously performed through a catheter inserted into the radial artery of the opposite side. Sampling was carried out every 15 sec from 0 to 2 min, every 30 sec from 2 to 5 min, every one min from 5 to 10 min, and 12, 14, 16, 20, 25, 30, 40, 50, and 60 min after the injection of ^{123}I-IMP. The fraction of true tracer activity in each arterial blood sample was examined

by the octanol extraction method, in which unmetabolized ^{123}I-IMP was extracted from the sample.[3,8,14] Then the standard input function was obtained as a relative pattern of Ca(t) by averaging the 10 subjects' normalized time-course data for Ca(t).

Simulation analysis

When the values of K_1 and k_2 (or V_d) are given and the standard input function is used, the relative pattern of Cb(t) can be simulated by solving differential Equation (1) based on the 2-compartment model. By using both of the relative patterns of Ca(t) and Cb(t), the values of K_1 can be calculated from Equation (4) based on the microsphere model. The calculated values of K_1 are compared with those given in the 2-compartment model; we can, therefore, evaluate the error (underestimation) of K_1 calculated by the microsphere method. We also examined the underestimation related to time t in Equation (4) and the values of K_1 and V_d given in the 2-compartment model. As this simulation analysis is based on only the standard input function, the accuracy of the function was investigated.

Subjects

To investigate clinically the underestimation of rCBF by the microsphere method, we performed both ^{123}I-IMP and ^{133}Xe inhalation SPECT studies on 11 patients with various cerebral diseases. All of them were non-smokers and had no heart or pulmonary disease. As far as possible, patients were selected who had no or minimal brain atrophy, to avoid the partial volume effect of SPECT for estimating the tissue fraction $\alpha \fallingdotseq 1$.

rCBF measurement by ^{133}Xe inhalation SPECT

^{133}Xe inhalation SPECT studies were performed with a ring-type SPECT scanner, Headtome SET-050 (Shimadzu, Kyoto, Japan), equipped with a high sensitivity collimator. A dose of 1110 MBq of ^{133}Xe (Daiichi Radioisotope Co., Tokyo, Japan) mixed with room air was inhaled for 1 min using a mouthpiece with the nose clipped and an exclusive circulation box (Anzai Co., Tokyo, Japan). SPECT data were acquired in 64×64 matrices for 7 min. rCBF was measured by the sequential picture method.[19] Images were reconstructed in 64×64 matrices using a filtered back-projection algorithm with a RAMP and Butterworth filter. The effective spatial resolution of the system was 23.2 mm FWHM at the center of the transaxial field of view, and the slice thickness was 10 mm. When measuring rCBF, we placed a total of 10 rectangular ROIs with 24×24 mm in size on both sides of the cerebellar hemisphere, frontal cortex, temporal cortex, occipital cortex and parietal cortex. Anatomical identification of each position was confirmed by superimposition of the SPECT films on the X-CT films that were taken at the same levels as the SPECT images.

rCBF measurement by the microsphere method

Approximately 60 min after ^{133}Xe inhalation SPECT, ^{123}I-IMP SPECT studies were performed with the same SPECT scanner equipped with a high resolution collimator. SPECT data were acquired from 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 of the system was 13.4 mm FWHM at the center of the transaxial field of view. Attenuation correction was done numerically by assuming an elliptical brain outline.[20]

Time t in Equation (4) for the microsphere method was set at 5 min. A dose of 222 MBq of ^{123}I-IMP was injected via a cubital vein for 1 min, and continuous withdrawal of arterial blood was simultaneously performed for 5 min through a catheter inserted into the radial artery of the opposite side. The fraction of true tracer activity of the arterial blood sample was examined by the octanol extraction method described above. The integral term $\int_0^{5\text{min}} C_a(s)ds$ in Equation (4) was then measured as previously reported.[21] The SPECT scan was performed from 25 min to 55 min after injection, and the value of Cb ($t=5$ min) in Equation (4) was calculated from the SPECT image as reported by Matsuda et al.[22]

RESULTS

When the values of K_1 and V_d were given at 0.5 (ml/g/min) and 30 (ml/g) in the 2-compartment model, the values of K_1 were calculated by the microsphere method following the injection of ^{123}I-IMP (Fig. 1a). The calculated values of K_1 decreased from the given value of 0.5 as time after injection increased. Fig. 1b indicates the % K_1 error up to 15 min as calculated by the microsphere method. The rate of underestimation of K_1 was found to be 4.6% at 5 min, 10.2% at 10 min and 15.1% at 15 min after injection.

The standard input function was shown to be valid (Fig. 2). The % error curve calculated by using the

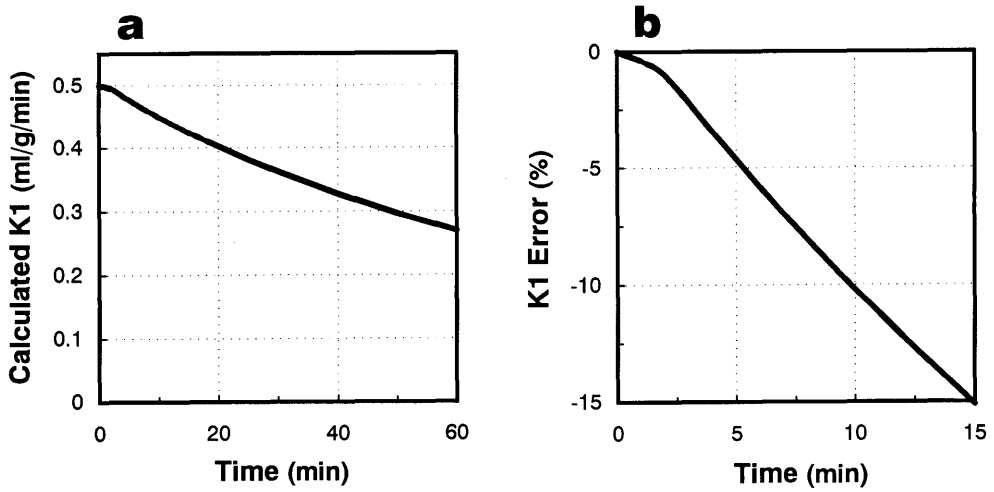

Fig. 1. Simulation study for the underestimation of K_1 calculated by the microsphere method in comparison with K_1 given at 0.5 (ml/g/min) in the 2-compartment model. Abscissa (**a**), (**b**): Time after injection of ^{123}I-IMP. Ordinate (**a**): Calculated K_1 (ml/g/min). Ordinate (**b**): % error of the calculated K_1.

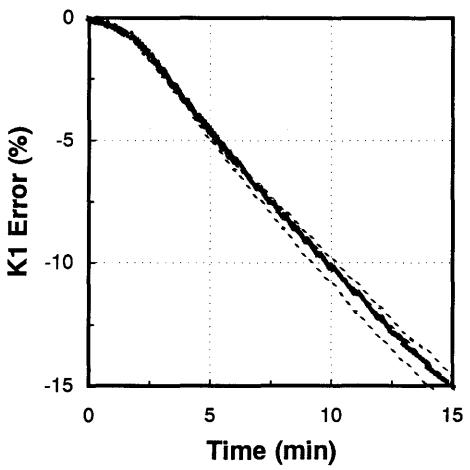

Fig. 2. Validation of the standard input function. The gray solid line represents the % error curve calculated by using the standard input function as shown in Fig. 1(**b**), and the five broken lines represent the respective curves calculated from the true input function of five subjects.

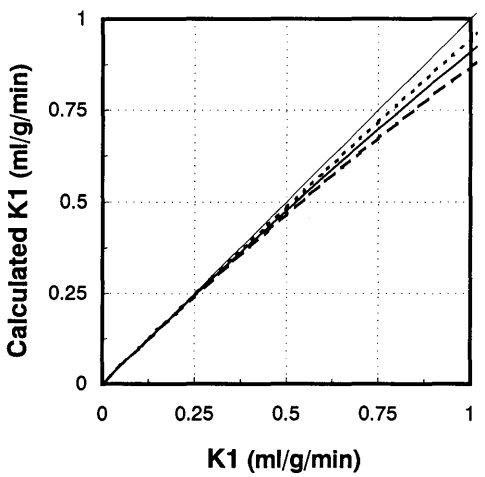

Fig. 3. K_1 (ordinate) calculated by the microsphere method 5 min after ^{123}I-IMP injection was compared with K_1 (abscissa) given in the 2-compartment model for various V_d: - - - - V_d=50, ——— V_d=30, - - - - V_d=20(ml/g). The fine, straight solid line shows the line of identity.

standard input function as in Fig. 1b was compared with those calculated by using the true input function of each of five subjects selected arbitrarily. The curves showed almost the same pattern up to 15 min. Compared with the curve calculated by using the standard input function, those calculated by using the true input functions showed that differences in % error were less than ±3.5% at 5 min, ±3.2% at 10 min and ±3.1% at 15 min.

At 5 min after the injection of ^{123}I-IMP, the values of K_1 calculated by the microsphere method were compared with those given in the 2-compartment model for various V_d (Fig. 3). K_1 was underestimated by the microsphere method with the increase in K_1 or decrease in V_d in the 2-compartment model. When the value of V_d was given at 30(ml/g), the rate of underestimation of K_1 by the microsphere method was found to be 2.4% at a given K_1 value of 0.25 (ml/

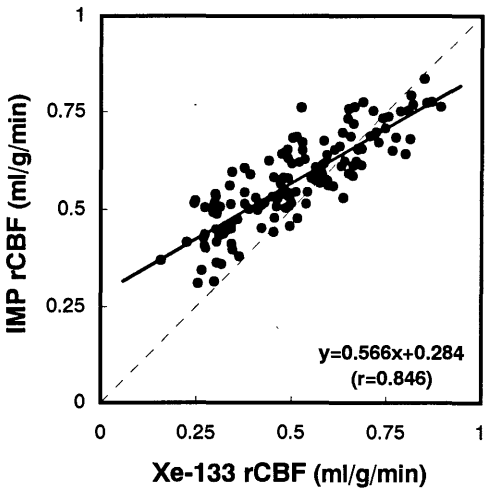

Fig. 4. Correlation of rCBF values obtained by the microsphere method with those by the ^{133}Xe inhalation method in various regions of 11 patients. The solid line denotes the results of the linear-regression analysis. The broken line shows the line of identity.

g/min), 4.6% at $K_1=0.5$ and 6.9% at $K_1=0.75$. At a given K_1 value of 0.5, the underestimation of K_1 was 2.8% at $V_d=50$, 4.6% at $V_d=30$ and 6.9% at $V_d=20$.

The values of rCBF measured by the microsphere method with ^{123}I-IMP in 11 patients were significantly correlated with those measured by the ^{133}Xe inhalation method (Fig. 4). Although the underestimation by the microsphere method was insignificant, the overestimation was observed more in low flow regions.

DISCUSSION

We were able to quantitatively assess underestimation by the microsphere method of rCBF (K_1) caused by the washout of ^{123}I-IMP from brain tissue. The rate of underestimation was determined to be 4.6% at 5 min, 10.2% at 10 min and 15.1% at 15 min after injection of the tracer. Since 4.6% is considered negligible in clinical studies, we concluded that the microsphere model could be applied to obtain accurate measurements of rCBF up to approximately 5 min.

As the influence of washout of ^{123}I-IMP from brain tissue was assumed to be negligible in the early phase after injection, the method of rCBF measurement based on the microsphere model with continuous withdrawal of arterial blood was developed.[3] This method, which has been considered accurate,[4,5] is commonly used in clinical studies. However, several reports have indicated that the microsphere method underestimates rCBF because of the washout of the tracer with increasing scan duration of SPECT.[5-7,12,13] Yonekura et al.[6] reported that, in comparison with analysis based on the 2-compartment model, the microsphere method could accurately estimate rCBF 5-10 min after injection, but as time increased, rCBF was underestimated. Murase et al.[7] indicated that even in the early phase after injection, the influence of washout could not be considered negligible. However, these studies on the underestimation of rCBF were based on clinical SPECT data, and therefore are considered to have been subject to various errors and influences. Clear, quantitative assessment has not been carried out, and therefore it is not known until how late the microsphere model accurately measures rCBF. In this study, using only the standard input function, we were able to perform a noise-free simulation based on the microsphere model and 2-compartment model. The accuracy of the standard input function was validated as in Fig. 2. It was therefore possible to evaluate the underestimation of rCBF by the microsphere method. That is, the results of the simulation were considered to indicate a theoretical defect of the microsphere model, and to be generally applicable to various studies of the microsphere model. However, if the true input function of a subject shows a quite different pattern compared with the standard input function due to a patient with heart or pulmonary disease or due to the different manner of injection of the tracer, the rate of underestimation of rCBF may change.

As previously reported,[6-8] it was found that the microsphere method underestimated rCBF as time after injection increased (Fig. 1). When the values of K_1 and V_d in the 2-compartment model were given at 0.5 (ml/g/min) and 30 (ml/g), which were considered to be approximately normal values,[5-8,22] the value of K_1 at 5 min after injection was calculated to be 4.6% lower by the microsphere method. Since an underestimate of 4.6% is considered negligible in clinical studies, we concluded that the microsphere model was acceptable for ^{123}I-IMP kinetics within approximately 5 min after injection; that is, the microsphere method could estimate rCBF with accuracy for up to 5 min. It was also quantitatively determined that the microsphere method underestimated rCBF with the increase in K_1 and decrease in V_d as given in the 2-compartment model (Fig. 3). The results shown in Figs. 1 and 3 are therefore useful to evaluate underestimation as it relates to time after injection and the values of K_1 and V_d. When the time for the microsphere method is chosen within 5 min, the underestimation of rCBF is considered negligible in the practical range of K_1 and V_d.

When the microsphere model is generally applied to the measurement of rCBF, it would not be acceptable to perform the SPECT during the first 5 min because of the poor activity accumulated in the brain tissue. The method reported by Matsuda et al.[22] is, therefore, used clinically. This method requires SPECT scan 30 min after injection of ^{123}I-IMP, and the SPECT image is corrected to the image at 5 min by using the monitored entire brain time-activity curve. This method can make the microsphere model possible to use routinely.[21,23-25] It is trace that further investigation of the error caused by the correction with the use of entire brain time-activity curve should be done. However, the results in this paper are also applicable to the study using the method of Matsuda et al.

In the 11 patients, the rCBF values measured by the microsphere method were not significantly underestimated compared with the ^{133}Xe inhalation method (Fig. 4). This suggests that the underestimation by the microsphere method, which was estimated as 4.6% by the simulation analysis, is clinically negligible. The slight underestimation observed in high flow regions seemed to confirm the simulation analysis. Rather than the underestimation, the overestimation by the microsphere method was observed more in low flow regions. This was considered to be due to the previously described, method of Matsuda et al. as reported by Takahashi et al.[24,25]

We were able to quantitatively assess the time-related underestimation of rCBF by the microsphere method. It was concluded that the microsphere model could be applied to rCBF measurement in clinical studies up to approximately 5 min after injection regardless of washout.

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* **21:** 940-946, 1989.
2) Winchell HS, Horst WD, Braun L, Oldendorf WH, Hattne Rr, Parker H: N-isopropyl-[^{123}I]p-iodoamphetamine: single-pass brain uptake and washout; binding to brain synaptosomes; and localization in dog and monkey brain. *J Nucl Med* **21:** 947-952, 1980.
3) Kuhl DE, Barrio JR, Huang SC, Selin C, Ackermann RF, Lear JL, Wu JL, Lin TH, Phelps ME: Quantifying cerebral blood flow by N-isopropyl-p-[^{123}I] iodoamphetamine (IMP) tomography. *J Nucl Med* **23:** 196-203, 1982.
4) Tsuda Y, Hartman A, Biersack HJ, Valerius E, Broich K, Reichmann K: Semiquantifying regional cerebral blood flow by ^{123}I-amphetamine (IMP) SPECT in cerebrovascular disorders: correlations with CBF indices by ^{133}Xe inhalation method. *Eur J Nucl Med* **14:** 546-551, 1988.
5) Greenberg JH, Kushner M, Rango M, Alavi A, Reivich M: Validation studies of iodine-123-iodoamphetamine as a cerebral blood flow tracer using emission tomography. *J Nucl Med* **31:** 1364-1369, 1990.
6) Yonekura Y, Nishizawa S, Mukai T, Iwasaki Y, Fukuyama H, Ishikawa M, Tamaki N, Konishi J: Functional mapping of flow and back-diffusion rate of N-isopropyl-p-iodoamphetamine in human brain. *J Nucl Med* **34:** 839-844, 1993.
7) Murase K, Tanada S, Mogami H, Kawamura M, Miyagawa M, Yamada M, Higashino H, Lio A, Hamamoto K: Validity of microsphere model in cerebral blood flow measurement using N-isopropyl-p-(I-123)iodoamphetamine. *Med Phys* **17:** 79-83, 1990.
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* **34:** 498-505, 1993.
9) Koppe RA, Holden JE, Raymond W: Performance comparison of parameter estimation techiques for the quantitation of local cerebral blood flow by dynamic positron computed tomography. *J Cereb Blood Flow Metabol* **5:** 224-234, 1985.
10) Patlak C, Blasberg R, Fenstermacher J: Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. *J Cereb Blood Flow Metabol* **3:** 1-7, 1983.
11) Takeshita G, Toyama H, Nakane K, Maeda H, Katada K, Takeuchi A, Koga S: Quantitative measurement of regional cerebral blood flow with I-123 IMP SPECT: A correction of the microsphere model by global extraction between artery and internal jugular vein. *Annals Nucl Med* **5:** 145-148, 1991.
12) Creutzig H, Schober O, Gielow P, Friedrich R, Becker H, Dietz H, Hundeshagen H: Cerebral dynamics of N-isopropyl-(^{123}I)p-iodoamphetamine. *J Nucl Med* **27:** 178-183, 1986.
13) Nishizawa S, Tanada S, Yonekura Y, Fujita T, Mukai T, Saji H, Fukuyama H, Miyoshi T, Harada K, Ishikawa M, Kikuchi H, Konishi J: Regional dynamics of N-isopropyl-(^{123}I)p-iodoamphetamine in human brain. *J Nucl Med* **30:** 150-156, 1989.
14) Iida H, Itoh H, Bloomfield PM, Munaka M, Higano S, Murakami M, Inugami A, Eberl S, Aizawa Y, Kanno I, Uemura K: A method to quantitate cerebral blood flow using a rotating gamma camera and iodine -123 iodoamphetamine with one blood sampling. *Eur J Nucl Med* **21:** 1072-1084, 1994.
15) Kety SS: The theory and application of the exchange of inert gas at the lung and tissue. *Pharmacol Rev* **3:** 1-41, 1951.
16) Huang SC, Carson RE, Hoffman EJ, Carson J,

MacDonald N, Barrio JR, Phelps ME: Quantitative measurement of local cerebral blood flow in humans by positron computed tomography and ^{15}O-water. *J Cereb Blood Flow Metabol* **3:** 141-153, 1983.

17) Iida H, Kanno I, Miura S, Murakami M, Takahashi K, Uemura K: A determination of the regional brain/blood partition coefficient of water using dynamic positron emission tomography. *J Cereb Blood Flow Metabol* **9:** 874-885, 1989.

18) Iida H, Hiroshi I, Nakazawa M, Hatazawa M, Nishimura H, Onishi Y, Uemura K: Quantitative mapping of regional cerebral blood flow using iodine-123-IMP and SPECT. *J Cereb Blood Flow Metabol* **9:** 874-885, 1994.

19) Kanno I, Lassen NA: Two methods for calculating regional cerebral blood flow emission computed tomography of inert gas concentrations. *J Comput Assist Tomogr* **3:** 71-76, 1979.

20) 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 Assist Tomogr* **5:** 216-226, 1981.

21) Odano I, Tsuchiya T, Nishihara M, Sakai K, Abe H, Tanak R: Regional cerebral blood flow measured with N-isopropyl-p-[^{123}I]iodoamphetamine and its redistribution in ischemic cerebrovascular disease. *Stroke* **24:** 1167-1172, 1993.

22) Matsuda H, Seki H, Sumiya H, Tsuji S, Tonami N, Hisada K, Fujii H, Kobayashi H: Quantitative cerebral blood flow measurement using N-isopropyl-(iodine 123) p-Iodoamphetamine and single photon emission computed tomography with rotating gamma camera. *Am J Physiol Imag* **1:** 186-194, 1986.

23) Takahashi N, Odano I, Nishihara M, Yuasa T, Sakai K: Regional cerebral blood flow measured with N-isopropyl-p-[^{123}I]iodoamphetamine single-photon emission tomography in patients with Joseph disease. *Eur J Nucl Med* **21:** 615-620, 1994.

24) Takahashi N, Ohkubo M, Odano I, Ohtaki H, Noguchi E, Yamazaki Y, Hatano M, Sakai K: A problem of quantitative measurement of regional cerebral blood flow using microsphere model and N-isopropyl-p-[^{123}I]iodoamphetamine (IMP): comparison with ^{133}Xe SPECT and sequential dynamic ^{123}I-IMP SPECT. *Jpn J Nucl Med* 31: 319-326, 1994.

25) Takahashi N: Quantifying regional cerebral blood flow with N-isopropyl-p-[^{123}I]iodoamphetamine by ring-type single-photon emission computed tomography: validity of a method to estimate early reference value by means of regional brain time-activity curve. *Ann Nucl Med* **4:** 253-258, 1994.