Extraction and Retention of Technetium-99m-ECD in Human Brain: Dynamic SPECT and Oxygen-15-Water PET Studies

Koichi Ishizu, Yoshiharu Yonekura, Yasuhiro Magata, Hidehiko Okazawa, Hidenao Fukuyama, Fumiko Tanaka, Naoya Hattori, Haruhiro Kitano, Toru Fujita, Nagara Tamaki and Junji Konishi

Departments of Nuclear Medicine and Neurology, Faculty of Medicine, Kyoto University, Kyoto; and Biomedical Imaging Research Center, Fukui Medical School, Fukui, Japan

The kinetic behavior of ^{99m}Tc-ethyl cysteinate dimer (^{99m}Tc-ECD) in the human brain was investigated in six normal volunteers. **Methods:** Dynamic SPECT and a three-compartmental model were used to estimate the rate constants of ^{99m}Tc-ECD in normal human brain. Extraction fraction (E), retention fraction (R) and permeability surface area product (PS product) of ^{99m}Tc-ECD were calculated using the rate constants. Regional cerebral blood flow (rCBF) was measured by PET with ^{15}O-water. **Results:** The rate constants in the cerebral cortex were estimated as 0.307 ± 0.021 for K1 (influx constant), 0.201 ± 0.047 for k2 (backdiffusion rate constant), 0.547 ± 0.103 for k3 (lipophilic-to-hydrophilic conversion constant) and 0.0028 ± 0.0012 for k5 (rate constant from lipophilic compartment to blood) at rCBF of 0.509 ± 0.055 ml/g/min (mean ± s.d.). The first-pass extraction, retention fraction and PS product were calculated as 0.608 ± 0.069, 0.734 ± 0.047 and 0.477 ± 0.060, respectively. The first- pass extraction of ^{99m}Tc-ECD decreased significantly with increases in rCBF. The retention fraction and PS product of ^{99m}Tc-ECD did not show significant changes within the normal range of rCBF. The net extraction of ^{99m}Tc-ECD calculated from the static SPECT image obtained from 20 to 40 min was 0.358 ± 0.039 in the cortex. **Conclusion:** Technetium-99m-ECD has a fairly high brain extraction, and its retention fraction and PS product appear to be independent of rCBF in the healthy human brain.

Key Words: technetium-99m-ECD; brain perfusion; SPECT; permeability surface area product

J Nucl Med 1996; 37:1600–1604

Technetium-99m-ethyl cysteinate dimer (^{99m}Tc-ECD) was developed as a retained-type brain perfusion tracer and has been widely used in clinical practice for visualizing regional blood flow in the human brain with SPECT (*1*). Technetium-99m-ECD is reported to have high in vitro stability (*2*) and rapid in vivo blood clearance (*3*). The regional distribution of ^{99m}Tc-ECD is reported to be well correlated with regional cerebral blood flow (rCBF) except in cerebrovascular disease with luxury perfusion (*4–6*). Although SPECT imaging of retained tracer in the brain provides a measure of the relative distribution of cerebral perfusion, absolute quantification of rCBF has been limited. This is partly because of the physical limitation of SPECT imaging in quantitative measurement, but the clarification of the kinetic behavior of ^{99m}Tc-ECD is also important for the accurate quantitative measurement of rCBF with ^{99m}Tc-ECD SPECT. In this study, the regional kinetic parameters of ^{99m}Tc-ECD in the normal human brain were estimated by means of the compartmental model analysis of the dynamic SPECT data and rCBF measured by ^{15}O-water PET.

Received Jul. 21, 1995; revision accepted Jan. 23, 1996.

For correspondence or reprints contact: Koichi Ishizu, MD, Department of Nuclear Medicine, Faculty of Medicine, Kyoto University, Shogoin, Sakyo-ku, Kyoto 606-01, Japan.

MATERIALS AND METHODS

Subjects

Six normal healthy male volunteers (age 20–36 yr) were studied. None had a history of neurological disorders or psychiatric diseases. All subjects gave written informed consent before participating in the study.

A small catheter was placed in both the cubital vein of the subject's right arm for administration of the tracer and in the left brachial artery for intermittent arterial blood sampling. The subject lay on the scanner bed in a resting state with eyes open and the patients head was immobilized in a head holder.

PET Study

A PET study with ^{15}O-water was performed just before the SPECT examination on the same day using a whole-body PET scanner, which provided 15 PET slices at 7 mm intervals (*7*). All scans were performed at a resolution of 9 mm FWHM in the transaxial plane and 6.5 mm in the axial direction. The field of view and the pixel size of the reconstructed images were 256 mm and 2 mm, respectively. Before emission scanning, transmission scanning was performed using a standard plate source of ^{68}Ge/^{68}Ga for the correction of photon attenuation.

For measurement of quantitative values of rCBF, approximately 740 to 1100 MBq (20 to 30 mCi) of ^{15}O-water were injected into the right cubital vein over 5–8 sec, and PET data were acquired for 120 sec. Oxygen-15-water was synthesized by a small cyclotron and an automated synthesis system installed at Kyoto University Hospital. Arterial blood samples were obtained manually from the left brachial artery; 1 ml of blood was sampled every 5 sec for the first minute and then every 10 sec for the rest of the session. To obtain the arterial input function in each subject, blood samples were immediately measured by a scintillation counter. Functional images of rCBF were calculated from the PET images and the individual arterial input curve (*8*).

SPECT Study

Technetium-ECD was prepared from a commercially supplied cold kit and [^{99m}Tc]pertechnetate was obtained from the molybdenum-technetium generator. Fifteen to 20 min after the ^{15}O-water PET scan, each subject was infused with 740 MBq (20 mCi) ^{99m}Tc-ECD diluted in 10 ml of saline solution delivered at a constant speed for 1 min using the infusion pump.

Serial dynamic SPECT scanning was performed for 40 min on a triple-head SPECT scanner with high-resolution, fan-beam collimators and 140 keV ± 10% photo window. SPECT data were acquired every 30 sec by continuous rotation of the detectors about 120° (40 steps/120°/30 sec). The raw projection data were added to make a total of 20 images (1 min × 10 frames, 2 min × 6 frames, 4 min × 4 frames). In addition, the static SPECT images were obtained by summation of 20 to 40 min data. All SPECT images were reconstructed by a filtered back-projection algorithm with a

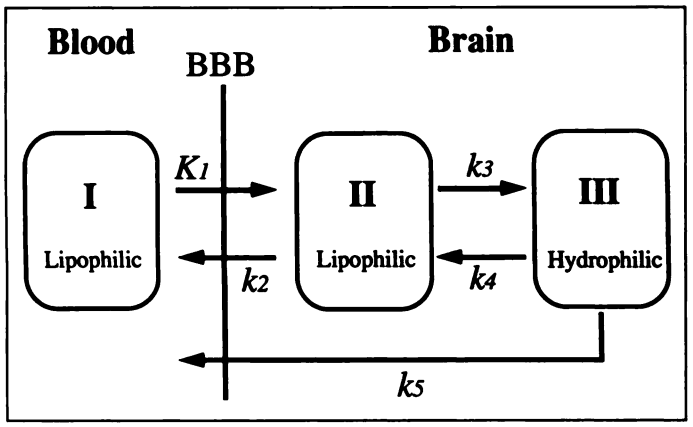

FIGURE 1. A kinetic model of ^{99m}Tc-ECD with model 3 compartments and 5 parameters. K1 to k5 are the rate constants for the transport of the tracer between compartments. The value of k4 is assumed to be zero in this study.

Butterworth filter (cutoff frequency 0.25, power factor 4) and displayed on a 64 × 64 matrix. The pixel size was 4.5 × 4.5 mm, and the slice thickness was 7.1 mm. Attenuation correction was performed by assuming the elliptical outline of the head in each slice and uniform attenuation.

In the ^{99m}Tc-ECD study, 2 ml of arterial blood were sampled manually every 15 sec for the first 90 sec and subsequently at 2, 3, 5, 7, 10, 20 and 40 min after injection. The sampled blood was then divided into two samples of 0.5 ml and 1.0 ml. The latter samples were immediately put directly into tubes containing 2.0 ml octanol, which were rapidly vortexed and centrifuged. The radioactivities of the supernatant and the other part of the sampled blood were then counted in the well counter. The ratio of radioactivity in the octanol phase to the total blood activity was calculated for each blood sample.

Data Analysis

Calibration of PET or SPECT images with arterial blood data was performed by cross-calibration of the PET or SPECT counts and the activity was measured with a scintillation counter. Cross-calibration of PET images was performed with ^{18}F solution, and that of SPECT images with ^{99m}Tc solution using a cylindrical phantom with 16 cm inner diameter.

To compare the PET and SPECT images in each subject accurately, we applied a three-dimensional adjustment of the two volumetric datasets using originally developed software on a Macintosh computer. A matrix conversion of the SPECT images

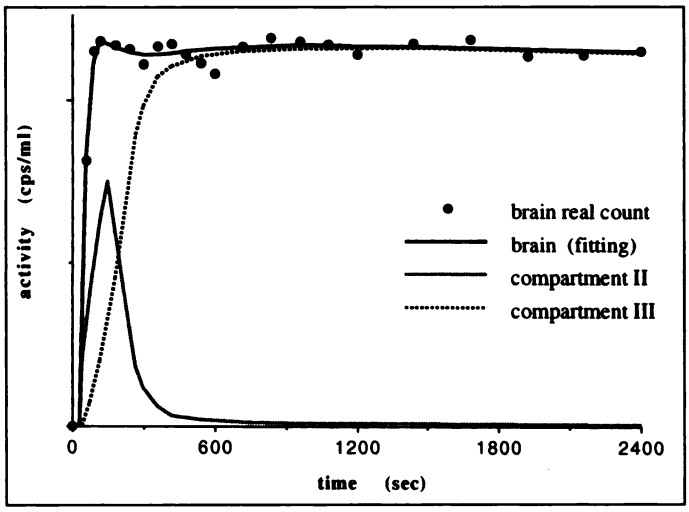

FIGURE 2. A typical time course of the ^{99m}Tc-ECD brain tissue activity and the fitted curves.

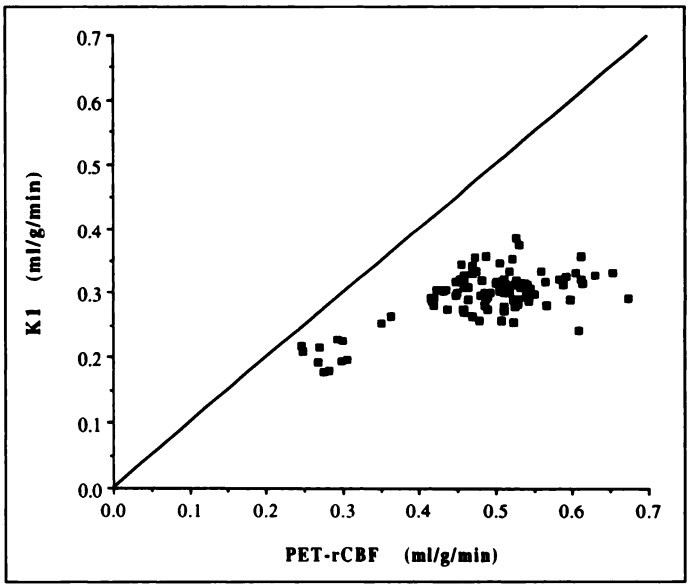

FIGURE 3. Comparison of K1 and rCBF measured by PET.

(from 64 × 64 to 128 × 128) was performed, and the pixel size of the PET images was adjusted to that of the SPECT images. Then both the PET and serial SPECT images were converted to three-dimensional images consisting of 1.75 mm voxels made by interpolation. The three-dimensional volumetric PET data were resliced to adjust them to the volumetric SPECT data.

Three tomographic slices, corresponding respectively to the levels of the centrum semiovale, basal ganglia and cerebellum, were selected from the adjusted PET and SPECT images for regional comparison. Regions of interest (ROI) were placed on the bilateral frontal cortex, parietal cortex, temporal cortex, occipital cortex, basal ganglia, thalamus, white matter and cerebellum. The arterial input of ^{99m}Tc-ECD was calculated by integrating the values of diffusable radioactivity over time.

Kinetic Model

To analyze the in vivo kinetic behavior of ^{99m}Tc-ECD, we used a kinetic model including three compartments and five parameters (Fig. 1). This model consists of the following three compartments: (a) the lipophilic tracer in the blood with the concentration of calcium (Ca); (b) the lipophilic tracer in the brain with the concentration of cerium (Ce); and (c) the hydrophilic tracer trapped in the brain with the concentration of curium (Cm), where Ca is the radioactivity per milliliter of arterial blood and Ce and Cm are the radioactivities per milliliter of brain tissue. K1 to k5 are the rate constants for the transport of the tracer between compartments. K1 is the influx constant, k2 is the back diffusion rate constant, k3 is the lipophilic-to-hydrophilic conversion constant and k4 is the hydrophilic-to-lipophilic conversion constant. The value of k4 is assumed to be zero in this study. As the kinetic analysis demonstrated a gradual decrease in brain activity, we defined the pathway from the lipophilic compartment to the blood as represented by the rate constant k5.

The set of equations describing our kinetic model is as follows:

$$dCe(t)/dt = K1 \cdot Ca(t) - (k2 + k3) \cdot Ce(t). \quad \text{Eq. 1}$$

$$dCm(t)/dt = k3 \cdot Ce(t) - k5 \cdot Cm(t). \quad \text{Eq. 2}$$

Ca(t) was expressed by the exponential curves fitted to the data of the serial arterial sampling.

TABLE 1
Rate Constants

	PET-rCBF (ml/g/min)	K1 (ml/g/min)	K2 (l/min)	k3 (l/min)	k5 (l/min)
Frontal	0.493 ± 0.055	0.307 ± 0.016	0.217 ± 0.046	0.542 ± 0.091	0.0026 ± 0.0011
Temporal	0.531 ± 0.061	0.302 ± 0.026	0.201 ± 0.045	0.512 ± 0.083	0.0030 ± 0.0015
Parietal	0.514 ± 0.052	0.305 ± 0.019	0.203 ± 0.047	0.551 ± 0.108	0.0023 ± 0.0012
Occipital	0.499 ± 0.041	0.312 ± 0.021	0.181 ± 0.041	0.584 ± 0.113	0.0031 ± 0.0008
Basal ganglia	0.490 ± 0.064	0.306 ± 0.020	0.197 ± 0.049	0.621 ± 0.190	0.0025 ± 0.0012
Thalamus	0.519 ± 0.055	0.290 ± 0.031	0.237 ± 0.110	0.496 ± 0.173	0.0023 ± 0.0009
Cerebellum	0.516 ± 0.059	0.328 ± 0.035	0.188 ± 0.044	0.536 ± 0.093	0.0029 ± 0.0015
White matter	0.292 ± 0.034	0.213 ± 0.029	0.151 ± 0.054	0.417 ± 0.108	0.0022 ± 0.0011

$$Ca(t) = a \cdot t \qquad (0 < t \leq t_p)$$
$$= g1 \cdot \exp(-l1 \cdot t) + g2 \cdot \exp(-l2 \cdot t) + g3 \cdot \exp(-l3 \cdot t). \qquad (t_p < t) \qquad \text{Eq. 3}$$

In these equations, a, g1, g2, g3, l1, l2 and l3 are the constants and tp is the peak time of the octanol-extracted ^{99m}Tc-ECD activity curve. Brain activity, Cb, is given as follows:

$$Cb(t) = Ce(t) + Cm(t). \qquad \text{Eq. 4}$$

Solving Equations 1 and 2 with the assumption that the initial concentrations and k4 are zero, we obtain

$$Ce(t) = K1 \cdot \exp[-(k2 + k3)t] * Ca(t). \qquad \text{Eq. 5}$$

$$Cm(t) = [K1 \cdot k3/(k2 + k3 - k5)]\{\exp(-k5 \cdot t) - \exp[-(k2 + k3)t]\} * Ca(t), \qquad \text{Eq. 6}$$

where * denotes the operation of convolution.

The rate constants (K1, k2, k3 and k5) were estimated in each ROI on the SPECT images by the least-squares curve fitting procedure by applying Newton-Raphson method (*9,10*).

The values of the first-pass extraction into compartment II (E) can be calculated from K1 and PET-rCBF (F):

$$E = K1/F. \qquad \text{Eq. 7}$$

The retention fraction (R) and the permeability-surface area product (PS) were calculated under the assumption of the ultimate value for PS product of water in the brain as follows:

$$R = k3/(k2 + k3 - k5). \qquad \text{Eq. 8}$$

$$PS = -F \cdot \ln(1 - K1/F). \qquad \text{Eq. 9}$$

In addition, the net extraction fraction (Enet) was calculated with the brain activity in the static SPECT image obtained from 20 to 40 min data and the integral of arterial radioactivity from injection start to the midtime of the scan, as follows:

$$Enet = Cb(20-40)/F \Big/ \int_0^{30} Ca(t)\,dt. \qquad \text{Eq. 10}$$

RESULTS

Figure 2 shows a typical time course of the brain tissue activity and the fitted curves. The brain activity reached a maximum value just after the completion of the tracer injection, and the blood activity showed a rapid decrease after the cessation of the infusion. The static image of ^{99m}Tc-ECD SPECT and ^{15}O-PET image demonstrated a similar distribution pattern, and no apparent abnormality was observed in any subject.

Table 1 shows the regional values of the rate constants. The rate constants in the cerebral cortex were 0.307 ± 0.021 for K1, 0.201 ± 0.047 for k2, 0.547 ± 0.103 for k3 and 0.0028 ± 0.0012 for k5 (means ± s.d.). Figure 3 shows the comparison of K1 and rCBF, demonstrating that K1 was considerably underestimated in comparison with rCBF. Table 2 shows the regional values of the kinetic parameters of ^{99m}Tc-ECD. The mean values of these parameters in the cortex were 0.509 ± 0.055 for rCBF, 0.608 ± 0.069 for first-pass extraction, 0.734 ± 0.047 for retention fraction, 0.477 ± 0.060 for PS product, and 0.358 ± 0.039 for net extraction fraction. The brain first-pass extraction of ^{99m}Tc-ECD decreased significantly with increases in rCBF as shown in Figure 4. The retention fraction, however, did not show significant changes within the measured normal range of rCBF (Fig. 5). There was no correlation between PS product and rCBF (Fig. 6). The decrease of the net extraction fraction of ^{99m}Tc-ECD was almost the same as that of the first-pass extraction with increases in rCBF as shown in Figure 7.

TABLE 2
K Complexes and Net Extraction

	PET-rCBF (ml/g/min)	First-pass extraction	Retention fraction	PS product (ml/g/min)	Net extraction
Frontal	0.493 ± 0.055	0.631 ± 0.076	0.716 ± 0.043	0.492 ± 0.059	0.361 ± 0.036
Temporal	0.531 ± 0.061	0.577 ± 0.078	0.721 ± 0.041	0.458 ± 0.076	0.333 ± 0.040
Parietal	0.514 ± 0.052	0.596 ± 0.049	0.732 ± 0.052	0.465 ± 0.039	0.355 ± 0.035
Occipital	0.499 ± 0.041	0.629 ± 0.049	0.766 ± 0.036	0.495 ± 0.049	0.381 ± 0.030
Basal ganglia	0.490 ± 0.064	0.633 ± 0.075	0.756 ± 0.044	0.491 ± 0.059	0.383 ± 0.045
Thalamus	0.519 ± 0.055	0.564 ± 0.071	0.687 ± 0.072	0.431 ± 0.064	0.311 ± 0.038
Cerebellum	0.516 ± 0.059	0.644 ± 0.096	0.743 ± 0.055	0.541 ± 0.106	0.379 ± 0.052
White matter	0.292 ± 0.034	0.733 ± 0.079	0.744 ± 0.061	0.395 ± 0.080	0.441 ± 0.066

PS product = permiability surface area product.

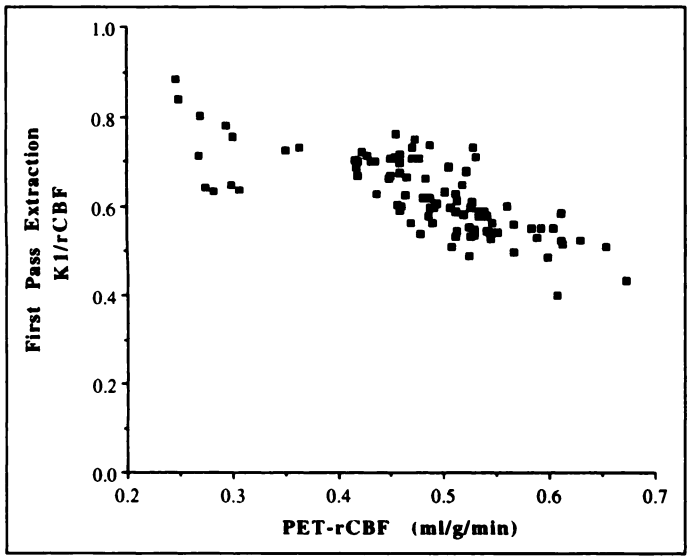

FIGURE 4. Relationship of the first-pass extraction of ^{99m}Tc-ECD and rCBF.

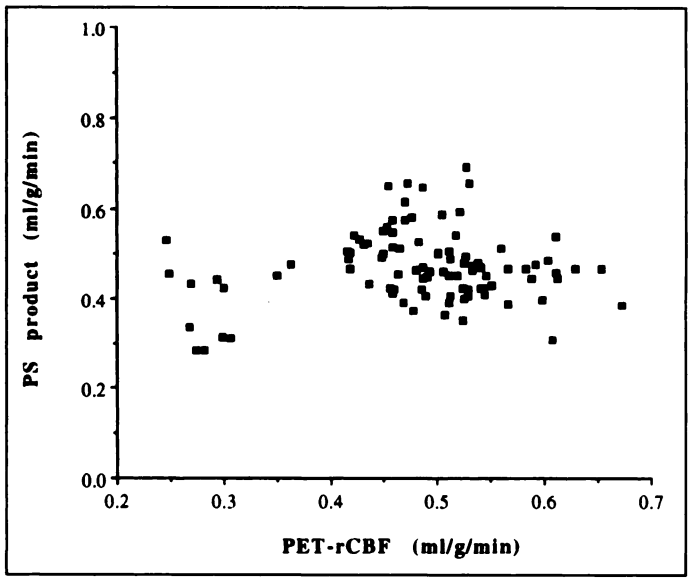

FIGURE 6. Relationship of the PS product of ^{99m}Tc-ECD and rCBF.

DISCUSSION

We used a kinetic model and dynamic SPECT to study the behavior of ^{99m}Tc-ECD in the human brain and the possibility of quantitative measurement of CBF with this tracer. A three-compartment model proposed by Friberg et al. (*11*) was applied to our human study in vivo. In this kinetic model, the value of the hydrophlic-to-lipophilic conversion constant k4 was assumed to be zero. Friberg et al. justified the assumption that k4 is negligible for practical purposes by the absence of any detectable redistribution in the comparison between the 1-hr and 24-hr images, indicating practically the same rate of loss in all regions. They also reported that the k5 value could not be ignored in the kinetic model because a slow loss of hydrophilic tracer or metabolites not subject to detectable reuptake in tissue was shown. As reported by Vallabhajosula et al. (*3*), the activity throughout the brain of ^{99m}Tc-ECD when injected as a bolus reaches a maximum at only 1 min postinjection, followed by some loss of activity and a plateau at about 2 min postinjection. Therefore, we injected ^{99m}Tc-ECD slowly for 1 min with an infusion pump instead of giving a bolus injection in order to acquire as much scan data as possible before the ^{99m}Tc-ECD activity reached the maximum, and not to omit the peak of arterial activity from arterial sampling.

The values of the kinetic parameters in our study are similar to those of other studies using different methods. Friberg et al. (*11*) reported that the average values of the kinetic parameters in the human whole brain measured in three subjects were K1 = 0.29, k2 = 0.22, k3 = 0.57, k5 = 0.0038, the first-pass extraction E = 0.60, and the retention fraction r = 0.73 at a mean flow value of 0.46 ml/g/min using an intracarotid ^{99m}Tc-ECD injection method and the ^{133}Xe inhalation SPECT study. Kundsen et al. (*12*) found E = 0.57 at a mean flow value of 0.53 ml/g/min using the intravenous double-indicator technique. The K1 value for ^{99m}Tc-d,l-hexamethyl-propylene amine oxime (^{99m}Tc-HMPAO) was reported to be 0.36 ml/g/min in the gray matter in four patients by Matsuda et al. (*13*) and 0.26 ml/g/min in 11 patients by Murase et al. (*14*).

The regional values of the kinetic parameters of ^{99m}Tc-ECD were compared with PET-rCBF data in our study. K1 showed a positive correlation with rCBF but it was considerably underestimated in comparison with rCBF. The first-pass extraction decreased significantly with increases in rCBF in the normal human brain. Kundsen et al. (*12*) and Rocco et al. (*15*) reported

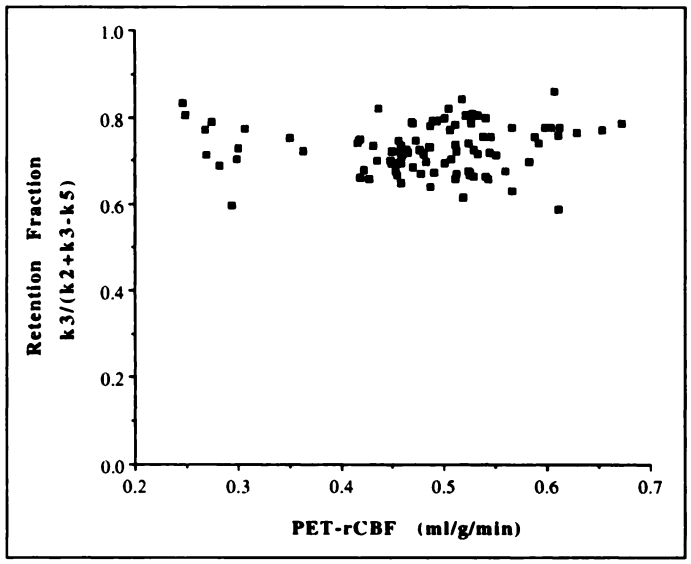

FIGURE 5. Relationship of the retention fraction of ^{99m}Tc-ECD and rCBF.

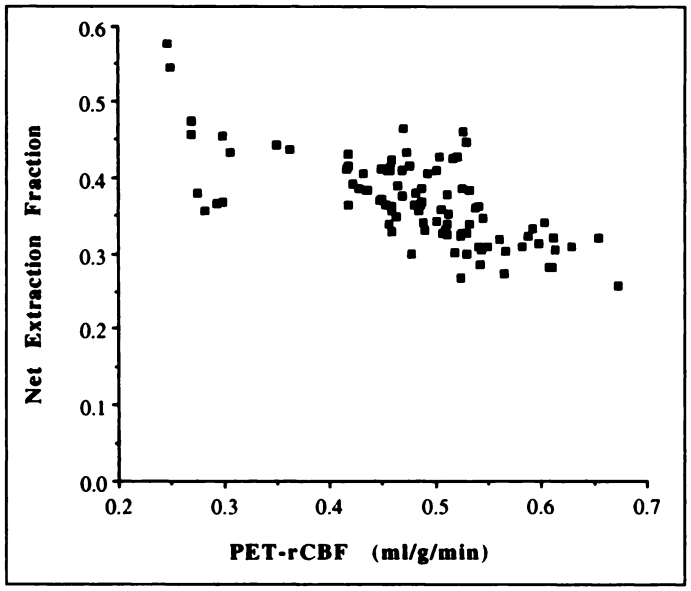

FIGURE 7. Relationship of the net extraction fraction of ^{99m}Tc-ECD calculated by SPECT counts from 20 to 40 min after injection and rCBF.

the same result in rat studies. This is the main reason for the nonlinearity between ^{99m}Tc-ECD uptake and rCBF (*5*) which is also observed in ^{99m}Tc-HMPAO (*16*). On the other hand, we found that the ^{99m}Tc-ECD retention fraction remained constant irrespective of changes in rCBF. Tanada et al. (*17*) reported that the retention fraction of ^{99m}Tc-ECD was independent of CBF in human brain study measured by ^{133}Xe method. This character of ^{99m}Tc-ECD is different from that of ^{99m}Tc-HMPAO, which shows a positive correlation between the retention fraction and rCBF (*14*). Additionally, PS product did not show a significant correlation with rCBF. Kundsen et al. (*12*) also reported similar findings in the rat brain, and their value in the human whole brain (0.48 ml/g/min) was exactly same as our value in the cerebral cortex. The present data, however, are limited to the normal physiological range of rCBF. Additional data in the higher flow range, which could be studied by acetazolamide challenge, will be necessary for further understanding of this tracer. In cerebrovascular disease, the kinetic parameters in the damaged brain tissue should be different from those obtained in the normal brain. Although the estimated kinetic parameters may not be directly applied to the pathological condition, these parameters should play a significant role in the quantitative measurement of rCBF.

Technetium-99m-ECD can be used to determine the individual input function by the serial arterial sampling and the octanol extraction technique because the conversion of lipophilic ^{99m}Tc-ECD to a nondiffusable tracer in the blood is not rapid like that of ^{99m}Tc-HMPAO (*18*). This is the most important advantage of ^{99m}Tc-ECD in quantitative measurement of rCBF. It is thought to be practically useful that the quantitative value of rCBF can be calculated with the static SPECT image, the integral of arterial input function of ^{99m}Tc-ECD radioactivity and the estimated mean value of net extraction fraction. For the accurate quantification of rCBF with ^{99m}Tc-ECD, the correction of decreased uptake of ^{99m}Tc-ECD in a high flow area should be considered. In ^{99m}Tc-HMPAO studies, Lassen's back-diffusion correction is widely used for the linearization (*18*), and it has also been applied for ^{99m}Tc-ECD. Because the relative decrease in ^{99m}Tc-ECD uptake in high blood flow areas is not related with its retention mechanism at the lipophilic-to-hydrophilic conversion but is directly due to the limited first-pass extraction from the blood into the brain, the linearization should be performed by a correction for the limited first-pass extraction. Therefore, the permeability-surface area product model with a constant value of 0.48 ml/g/min may be applicable for correction of the nonlinearity of ^{99m}Tc-ECD uptake.

CONCLUSION

Compartmental model analysis of ^{99m}Tc-ECD revealed that first-pass extraction was fairly high but flow-limited, and that the retention fraction and the permeability-surface area product are independent of rCBF in the healthy human brain.

ACKNOWLEDGMENT

This work was supported in part by a Research Grant for Nervous and Mental Disorders from the Japanese Ministry of Health and Welfare.

REFERENCES

1. Walovitch RC, Hill TC, Garrity ST, et al. Characterization of technetium-99m-L,L-ECD for brain perfusion imaging, part 1: pharmacology of technetium-99m-ECD in nonhuman primates. *J Nucl Med* 1989;30:1892–1901.
2. Walovitch RC, Francesch M, Picard M, et al. Metabolism of ^{99m}Tc-L,L-ethyl cysteinate dimer in healthy volunteers. *Neuropharmacology* 1991;30:283–292.
3. Vallabhajosula S, Zimmerman RE, Picard M, et al. Technetium-99m-ECD: a new brain imaging agent: in vivo kinetics and biodistribution studies in normal human subjects. *J Nucl Med* 1989;30:599–604.
4. Tsuchida T, Nishizawa S, Yonekura Y, et al. SPECT images of technetium-99m-ethyl cysteinate dimer in cerebrovascular diseases: comparison with other cerebral perfusion tracers and PET. *J Nucl Med* 1994;35:27–31.
5. Yonekura Y, Tsuchida T, Sadato N, et al. Brain perfusion SPECT with ^{99m}Tc-bicisate: comparison with PET measurement and linearization based on permeability-surface area product model. *J Cereb Blood Flow Metab* 1994;14:S58–S65.
6. Shishido F, Uemura K, Murakami M, et al. Cerebral uptake of ^{99m}Tc-bicisate in patients with cerebrovascular disease in comparison with CBF and $CMRO_2$ measured by positron emission tomography. *J Cereb Blood Flow Metab* 1994;14:S66–S75.
7. Sadato N, Yonekura Y, Senda M, et al. Measurement of regional cerebral blood flow change with $H_2{}^{15}O$ and positron emission tomography using a mechanical injector and a standard arterial input function. *IEEE Trans Med Imag* 1993;12:703–710.
8. Raichle ME, Martin WRW, Herscovitch P, Mintun MA, Markham J. Brain blood flow measured with intravenous $H_2{}^{15}O$. II. Implementation and validation. *J Nucl Med* 1983;24:790–798.
9. Marquardt DW. An algorithm for least-squares estimation of nonlinear parameters. *J Soc Int Appl Math* 1963;11:431–441.
10. Dell RB, Sciacca R, Lieberman K, Case DB, Cannon PJ. A weighted least-squares technique for the analysis of kinetic data and its application to the study of renal ^{133}Xe washout in dogs and man. *Circ Res* 1973;32:71–84.
11. Friberg L, Andersen AR, Lassen NA, Holm S, Dam M. Retention of ^{99m}Tc-bicisate in the human brain after intracarotid injection. *J Cereb Blood Flow Metab* 1994;14:S19–S27.
12. Knudsen GM, Andersen AR, Somnier FE, et al. Brain extraction and distribution of ^{99m}Tc-bicisate in humans and in rats. *J Cereb Blood Flow Metab* 1994;14:S12–S18.
13. Matsuda H, Oba H, Seki H, et al. Determination of flow and rate constants in a kinetic model of ^{99m}Tc-hexamethyl-propylene amine oxime in the human brain. *J Cereb Blood Flow Metab* 1988;8:S61–S68.
14. Murase K, Tanada S, Fujita H, et al. Kinetic behavior of technetium-99m-HMPAO in the human brain and quantification of cerebral blood flow using dynamic SPECT. *J Nucl Med* 1992;33:135–143.
15. Rocco RJD, Silva DA, Kuczynski BL, et al. The single-pass cerebral extraction and capillary permiability-surface area product of several putative cerebral blood flow imaging agents. *J Nucl Med* 1993;34:641–648.
16. Yonekura Y, Nishizawa S, Mukai T, et al. SPECT with [^{99m}Tc]-d,l-hexamethyl-propylene amine oxime (HMPAO) compared with regional cerebral blood flow measured by PET: effects of linearization. *J Cereb Blood Flow Metab* 1988;8:S82–S89.
17. Tanada S, Murase K, Inoue T, et al. In vivo comparison of intracerebral behavior of ^{99m}Tc-labeled ECD with ^{99m}Tc-HMPAO using dynamic brain SPECT and a compartment model analysis. *J Cereb Blood Flow Metab* 1991;11:S769.
18. Sharp PF, Smith FW, Gemmell HG, et al. Technetium-99m-HMPAO stereoisomers as potential agents for imaging regional cerebral blood flow: human volunteer studies. *J Nucl Med* 1986;27:171–177.