Clinical Application and Quantitative Evaluation of Generator-Produced Copper-62-PTSM as a Brain Perfusion Tracer for PET

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Copper-62-pyruvaldehyde bis(N^4-methylthiosemicarbazone) copper II (^{62}Cu-PTSM) has been proposed as a generator-produced positron-emitting tracer for perfusion imaging. To evaluate the characteristics of ^{62}Cu-PTSM as a cerebral perfusion tracer, brain PET images of ^{62}Cu-PTSM were compared with cerebral blood flow (CBF). **Methods:** Following an intravenous injection of ^{62}Cu-PTSM, a serial dynamic PET scan was performed for 10 min with arterial sampling in 10 subjects. CBF was measured by ^{15}O-labeled water before the ^{62}Cu-PTSM study. **Results:** Dynamic PET scan with octanol-extracted arterial input function indicated the presence of significant back-diffusion of ^{62}Cu-PTSM from the brain within 3 min after injection, followed by stable activity from 3 to 10 min. Comparison with ^{15}O-water PET demonstrated less contrast between high- and low-flow regions in ^{62}Cu-PTSM image and a nonlinear relationship of flow and ^{62}Cu-PTSM uptake, which suggests the underestimation of CBF in high-flow regions due to the existence of back-diffusion. **Conclusion:** Although ^{62}Cu-PTSM can be used widely for evaluation of brain perfusion with PET, kinetic analysis and correction may be needed to quantify regional CBF.

Key Words: copper-62-PTSM; PET; cerebral blood flow; perfusion tracer

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Generator-produced radiopharmaceuticals for PET are expected to play an important role for wide clinical applications of PET imaging without the necessity of an in-house cyclotron. Copper (II) pyruvaldehyde bis(N^4-methylthiosemicarbazone) labeled with ^{62}Cu (^{62}Cu-PTSM), which is obtained from the ^{62}Zn/^{62}Cu positron generator system, has been proposed as a promising perfusion tracer (*1,2*). Although this tracer demonstrated excellent cerebral perfusion images (*3*), quantitive measurement of cerebral blood flow (CBF) with ^{62}Cu-PTSM in clinical studies has not been reported yet.

It was postulated that the initial uptake of ^{62}Cu-PTSM is probably due to the diffusion of the intact lipophilic complex across the cell membrane followed by the reduction of copper (II) to copper (I) in the cell (*4*). This reduced copper is likely to be trapped in the cell by binding to intracellular macromolecules. On the other hand, most of the radioactivity in the blood a few minutes after intravenous injection of ^{62}Cu-PTSM is due to metabolites or other components that cannot penetrate the blood-brain barrier (*2,5*). Therefore, the arterial input of ^{62}Cu-PTSM is likely to be completed within a short period after the injection. However, the kinetic properties of this tracer have not been established, and it has not been proved that the reduction of copper occurs immediately without back-diffusion of the original intact compound.

The aim of this study was to examine the kinetic properties of ^{62}Cu-PTSM in human brain and evaluate the clinical applicability of this tracer for brain perfusion studies with PET. For this purpose, PET scans were performed using ^{15}O-water and ^{62}Cu-PTSM with arterial sampling in 10 subjects, and the ^{62}Cu-PTSM images were compared with the regional CBF (rCBF) images obtained by ^{15}O-water PET.

MATERIALS AND METHODS

Preparation of Zinc-62/Copper-62 Generator and Copper-62-PTSM

Zinc-62 was obtained by ^{63}Cu(p,2n)^{62}Zn nuclear reaction using natural copper (^{63}Cu 69.2%) as a target material. A ^{62}Zn/^{62}Cu generator was prepared with $^{62}ZnCl_2$ aqueous solution (1.1 GBq, pH 5.0) by the method reported previously (*6*). In this generator system, cation-exchange resin was packed into a column, and ^{62}Zn solution (1.1 GBq, in 2 ml of water, pH 5.0) was loaded to adsorb ^{62}Zn. A glycine solution (200 m*M*) was used as the eluant, and ^{62}Cu-glycine complex was obtained in glycine solution. PTSM was prepared as described previously (*7*). The ^{62}Cu-PTSM was quantitatively obtained by simple mixing of the generator eluate, ^{62}Cu-glycine and PTSM solution for a few seconds by a ligand-exchange reaction (*8*). After preparation of the generator, eluate was able to be acquired with the interval of every 40 to 60 min.

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The elution efficiency was 60% to 70%, and the radiochemical purity was greater than 95%. The product was acquired in a total volume of 4 ml of ^{62}Cu-PTSM (0.1 m*M* PTSM in 5% dimethyl sulfoxide) with glycine solution.

Subjects

The study involved 10 patients (5 male and 5 female, age range 18–75 yr). They all had various neurologic symptoms and were required to undergo PET scans for assessment of rCBF. The study was approved by the Ethical Committee of Kyoto University Faculty of Medicine, and written informed consent was obtained from all the patients before the PET study.

PET

The PCT-3600W system (Hitachi Medical Co., Tokyo, Japan) was used as a PET imaging device (*9*). This system permits the simultaneous acquisition of 15 transverse slices with a center-to-center distance of 7 mm. All scans were performed at a resolution of 9-mm full width at half maximum in the transaxial direction and 6.5 mm in the axial direction. The field of view and pixel size of the reconstructed images were 256 mm and 2 mm, respectively.

The subject's head was immobilized with an individually molded head holder. A small cannula was placed in the left brachial artery for serial blood sampling. Prior to all emission measurements, tomographic transmission data were obtained using a standard plate source of ^{68}Ge/^{68}Ga for attenuation correction. The tissue activity concentration in the PET images was cross calibrated against the well counter using a cylindrical phantom filled with ^{18}F solution.

To compare ^{62}Cu-PTSM images with rCBF, approximately 30 mCi of ^{15}O-water was injected into the right cubital vein over 5 to 8 sec, and PET data were acquired for 120 sec.

Ten to 15 min after ^{15}O-water scan, 10 to 21 mCi of ^{62}Cu-PTSM was injected intravenously over 5 to 8 sec in a total volume of 4 ml. PET data acquisition was started at the time of ^{62}Cu-PTSM injection and continued for 10 min in 15-sec frames for the first 120 sec and in 60-sec frames for the next 8 min. In addition to the serial dynamic PET images, static images of 2 to 10 min after injection were reconstructed from dynamic scan data.

Measurement of Arterial Blood Radioactivity

Arterial blood samples were obtained manually from the left brachial artery in each study from the time of injection to the end of the scan. In the ^{15}O-water study, 1 ml of blood was sampled every 4 to 5 sec for the first minute and then every 10 to 15 sec for the rest of the session. The blood samples thus obtained were immediately measured by the scintillation counter to obtain the arterial radioactivity. In the ^{62}Cu-PTSM study, 2 ml of blood was sampled as the same timing as in the ^{15}O-water study for the first 2 min and then sampled at 3, 5 and 10 min after injection. The sampled blood was then divided into two samples of 0.5 and 1.5 ml. The latter samples were immediately put directly into tubes containing octanol, which were rapidly vortexed and centrifuged. The supernatant in these tubes and the other part of the sampled blood (0.5 ml) were counted in a well counter. The ratio of radioactivity in the octanol phase to the total blood activity was calculated for each blood sample. To confirm that the radioactivity in the supernatant was in the original form of ^{62}Cu-PTSM, samples were analyzed by high-performance liquid chromatography (HPLC) in one case.

Data Analysis

The rCBF images were calculated from ^{15}O-water PET data in each subject using an autoradiographic method (*10,11*). Tissue activity images of ^{62}Cu-PTSM were reconstructed from the serial dynamic PET data. These tissue activity images and blood activity were corrected for physical decay of ^{62}Cu (half-life 9.74 min). To compare ^{62}Cu-PTSM images with rCBF obtained from ^{15}O-water data, counts were obtained from the same regions of interest (ROIs) in both PET images.

To examine the kinetic properties of ^{62}Cu-PTSM, the ROI was placed to include a whole-brain slice in serial dynamic PET images and rCBF PET image. If it is assumed that no back-diffusion of the tracer from the brain occurred, the regional tissue activity of ^{62}Cu-PTSM [C(t)] can be expressed by the following simple equation:

$$C(t) = F \cdot E(0) \int_0^t Ca(\tau)\, d\tau, \qquad \text{Eq. 1}$$

where F is rCBF, E(0) is the first-pass extraction and Ca(t) denotes the arterial input function. However, because the kinetic behavior of ^{62}Cu-PTSM in the brain is unknown, the temporal changes of net extraction [E(t)] were examined initially based on Equation 1.

$$C(t) = F \cdot E(t) \int_0^t Ca(\tau)\, d\tau, \qquad \text{Eq. 2}$$

$$E(t) = \frac{C(t)}{F \cdot \int_0^t Ca(\tau)\, d\tau}. \qquad \text{Eq. 3}$$

E(t) was estimated from rCBF values measured by ^{15}O-water PET (F), regional tissue activity of ^{62}Cu-PTSM [C(t)] and octanol-extractable lipophilic activity [Ca(t)] using Equation 3. The time differences between the arterial activity data and PET data were corrected by fitting the arterial curves to brain activity curves obtained from PET data for 3 to 5 sec of time delay. The monitoring curve of the tissue activity in the head was used for the correction of time delay in each patient.

For regional comparison of static ^{62}Cu-PTSM images and rCBF PET images, ROIs were placed in small square areas (12 × 12 mm) on multiple regions in the brain. Seventy-seven ROIs were placed in each subject. F·E values of ^{62}Cu-PTSM were calculated according to the following equation, which was modified from Equation 2,

$$F \cdot E = \frac{C_{ST}}{\int_0^t Ca(\tau)\, d\tau}, \qquad \text{Eq. 4}$$

where C_{ST} was the tissue activity obtained from the static ^{62}Cu-PTSM images reconstructed from the dynamic data of 2 to 10 min after injection. Because brain activity was stable during this period (2–10 min), C_{ST} was considered to be the final retained activities, and the arterial integral values to the midscan time of C_{ST} (6 min) were used for the calculation of F · E. To normalize the individual variation of retention fraction, the F · E values calculated above were divided by the net-extraction ratio obtained from the average E(t) value ($\bar{E}$) of 2 to 10 min in each subject.

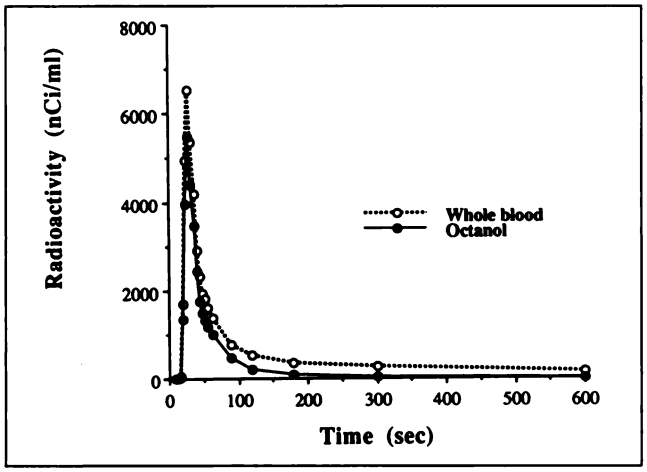

FIGURE 1. Representative time-activity curves of total blood (dashed line) and octanol-extractable activity (solid line) of ^{62}Cu-PTSM obtained by sampling directly from the brachial artery. The arterial radioactivity showed rapid clearance, and the lipophilic activity was almost negligible about 3 min after injection.

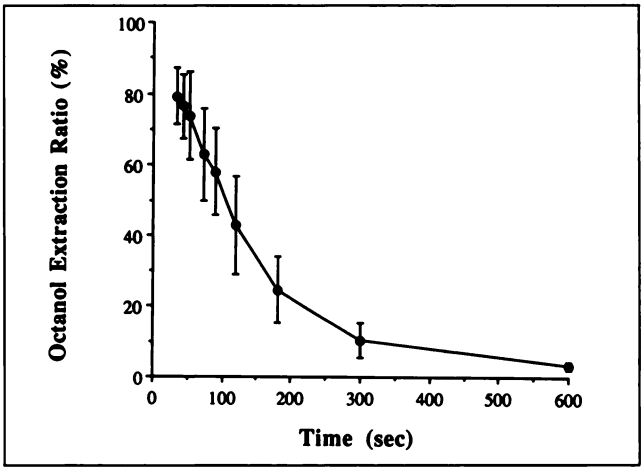

FIGURE 2. Average percentage of octanol extraction ratio of ^{62}Cu-PTSM in arterial blood samples (mean ± s.d.) obtained from 10 subjects. The percentage of ^{62}Cu-PTSM associated radioactivity in blood decreased rapidly.

$$F = \frac{C_{ST}}{\bar{E} \cdot \int_0^t Ca(\tau)\, d\tau}. \qquad \text{Eq. 5}$$

RESULTS

Arterial Blood Analysis

Figure 1 shows representative time-activity curves of total blood activity and octanol-extractable ^{62}Cu-PTSM activity in the arterial blood. The arterial blood activity reached a peak value within 40 sec, followed by rapid clearance. The octanol-extractable ^{62}Cu-PTSM activity showed faster clearance because of the rapid conversion of ^{62}Cu-PTSM to the hydrophilic compounds. The lipophilic activity was almost negligible 3 min after the injection. Figure 2 shows the average percentage of octanol-extracted ^{62}Cu-PTSM in the blood to the total blood activity in all studies as a function of time after intravenous injection, demonstrating rapid disappearance of ^{62}Cu-PTSM from the blood activity. HPLC analysis of the supernatant confirmed that the radioactivity in the octanol phase was in the original form of Cu-PTSM.

PET Images

Figure 3 shows a typical time-activity curve in the whole slice of the brain obtained from the tissue activity images reconstructed from the serial dynamic PET scan after ^{62}Cu-PTSM administration. Brain activity reached maximum value within 2 min, and tissue activity remained constant thereafter. Figure 4 shows the average net-extraction ratio (E(t) in Equation 3), which was calculated from the arterial input function obtained from the octanol-extractable ^{62}Cu-PTSM activities and rCBF measured by ^{15}O-water PET. The initial extraction was estimated to be approximately 80% (0.78 ± 0.10), followed by rapid decrease for 2 to 3 min reaching the plateau level at about 45% (0.45 ± 0.10).

Figure 5 shows the comparison of the values of static ^{62}Cu-PTSM PET image normalized by the arterial input function (F · E in Equation 4) and rCBF measured by ^{15}O-water PET. These values were obtained from the same ROIs placed on various regions of the ^{15}O-water PET image. These data clearly demonstrate the underestimation of ^{62}Cu-PTSM for the evaluation of rCBF, and the slopes of regression lines varied in each patient. The tendency to roll off at high flow was also noted. In Figure 6, the F · E values were corrected with the retention fraction of each patient (F in Equation 5) in which the plateau value of net extraction was used as the final retention value ($\bar{E}$ in Equation 5). Intersubject variation was diminished, and an excellent correlation was observed.

Figure 7 represents comparison of ^{62}Cu-PTSM and rCBF image in a patient with cerebral infarction. Com-

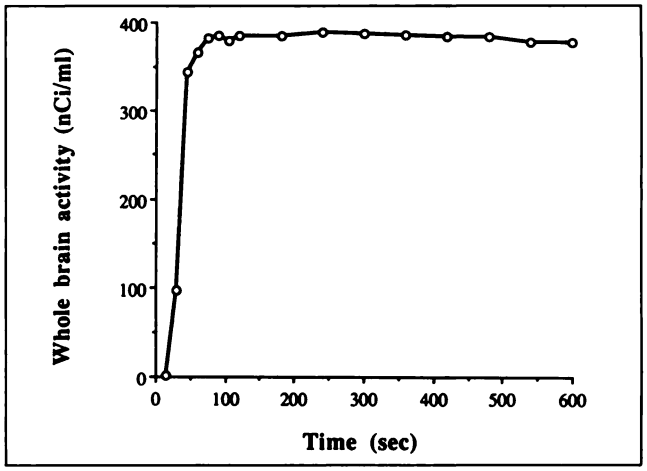

FIGURE 3. Time-activity curve of whole brain obtained from serial dynamic PET scan. The maximal radioactivity was observed within 2 min, followed by the stable tissue activity for a 10-min dynamic scan.

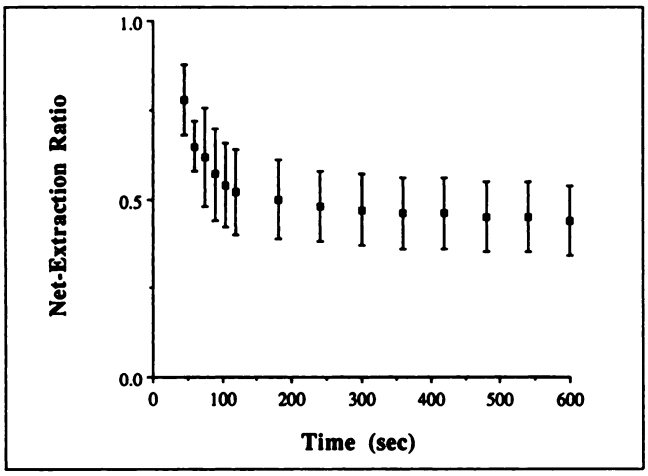

FIGURE 4. Temporal changes of net extraction measured in the whole brain (mean ± s.d.). The initial extraction of ^{62}Cu-PTSM was approximately 80% (0.78 ± 0.10), but net extraction decreased to a plateau value of 45% (0.45 ± 0.10).

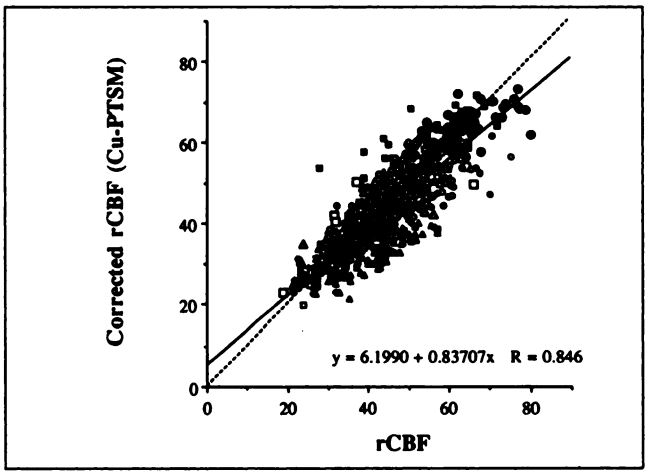

FIGURE 6. Relationship between estimated rCBF values corrected with net extraction of ^{62}Cu-PTSM in each subject and rCBF obtained by ^{15}O-water PET. Intersubject variation has disappeared. Linear-regression analysis (solid line) showed an excellent correlation. Dashed line is the line of identity.

pared with the rCBF image, which demonstrates well-defined, clear reduction of cerebral perfusion in the left hemisphere, the static image of ^{62}Cu-PTSM is slightly vague, demonstrating less contrast between high- and low-flow regions.

DISCUSSION

The purpose of this study was to evaluate the clinical applicability of ^{62}Cu-PTSM as a cerebral perfusion tracer for PET and examine the possibility of quantifying rCBF. Copper-62-PTSM has been proposed as a new generator-produced perfusion tracer for PET, however a few problems have appeared that need to be solved before clinical use. First, simplicity of the milking and labeling technique is required, and this point seems to have already been satisfied by two methods. One is the automated remote system for the synthesis of ^{62}Cu-PTSM presented by Mathias et al. (*12*), and the other is the new generator system and labeling method using a ligand-exchange reaction presented by Fujibayashi's group (*6,8*). The latter method was used in this study to obtain ^{62}Cu-PTSM solution with an interval of every 40 to 60 min. This simple preparation technique in a short period was suitable for a clinical study.

The second problem of this tracer is the difficulty in quantitation of blood flow because of the contaminated arterial blood activity by the metabolites or other components of ^{62}Cu binding. Estimation of the accurate input function is essential for quantitation of rCBF with ^{62}Cu-PTSM. For quantitation of myocardial perfusion, Herrero et al. (*13*) presented the octanol-extractable part of ^{62}Cu-PTSM as the corrected arterial input function in five dogs. They compared the values obtained from ^{62}Cu-PTSM and

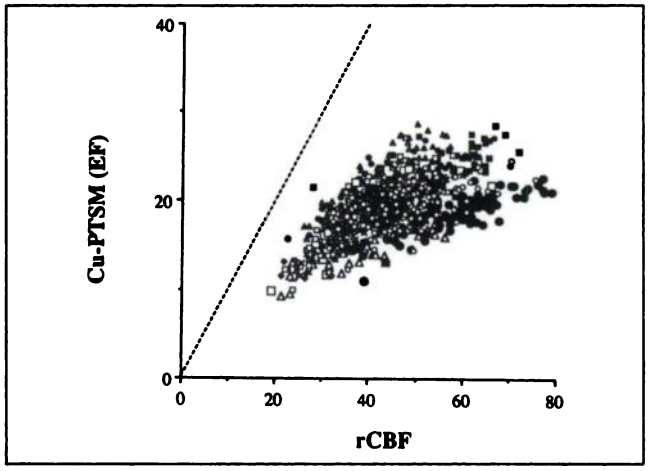

FIGURE 5. Comparison of fractional uptake of ^{62}Cu-PTSM and rCBF measured by ^{15}O-water PET. Datasets of each subject are shown by different symbols. Some tendencies of underestimation by ^{62}Cu-PTSM in high-flow regions and intersubject variation are shown. Dashed line is the line of identity.

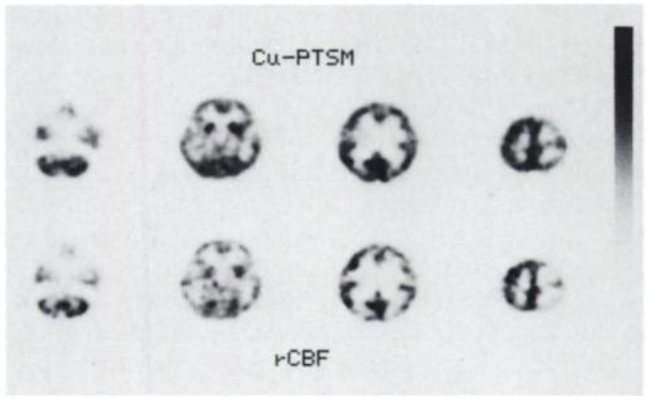

FIGURE 7. Static ^{62}Cu-PTSM PET images obtained 2 to 10 min after administration (top) and corresponding rCBF images obtained by ^{15}O-water PET (bottom) in a patient with cerebral infarction. Copper-62-PTSM showed slightly less contrast between normal and low-flow regions.

^{15}O-water images with those obtained from microspheres and demonstrated the slight underestimation of myocardial blood flow with ^{62}Cu-PTSM. A similar technique was used here to estimate the arterial input function to the brain. In the present study, the first-pass extraction fraction estimated from the initial uptake ratio of ^{62}Cu-PTSM to the brain's blood flow (0.78 ± 0.10) was similar to that in a previous report (*14*). However, the net extraction in the brain decreased gradually and reached stable values at 3 to 4 min. The final net-extraction values (0.45 ± 0.10) were apparently lower than the initial extraction. This result is consistent with a residual fraction for ^{67}Cu-PTSM found in an isolated rabbit heart perfusion study by Shelton et al. (*15*).

Equation 2 shows that E does not mean constant extraction but rather temporal changes of fractional uptake, as shown in Figure 4. The gradual decrease in net extraction of ^{62}Cu-PTSM was similar to the case of [^{99m}Tc]-d,l-hexamethylpropyleneamine oxime (HMPAO) (*16*). Although Shelton et al. (*15,17*) reported that the reduction of copper(II) to copper(I) is almost instantaneous after crossing the cell membrane and no backdiffusion occurs, as in an accurate microsphere model, the result in this study proved the existence of a backflux part of this tracer. Mathias et al. (*5*) measured the extraction fraction and "trapped fraction" of ^{67}Cu-PTSM using the single-pass method in the baboon brain. They reported a high initial extraction of 0.81, but the "trapped fraction" was decreased to 0.59, indicating the existence of back-diffusion. The present study demonstrated similar values for the initial extraction but slightly lower net extraction than the previous data in the baboon brain. The difference might be related to the retention mechanism of Cu-PTSM. Similar to the report by Mathias et al. (*5*), the permeability-surface area product (PS) can be estimated using the extraction and rCBF obtained in this study, although it may not be accurate because of the limited number of datasets. The PS estimated by initial extraction was approximately 62 ml/min/100 g on average, which was lower than the baboon data.

Regarding the retention mechanism of this tracer, Fujibayashi et al. (*18*) reported that the irreversible reduction was specifically initiated by the mitochondrial enzymatic system in murine brain. If the reduction occurs in cytosol by sulfhydryl groups, as described in the tumor cell models (*4*), the trapping of ^{62}Cu may be immediate without back-diffusion. However, in the normal brain, the backflux of intact tracer was observed, which may prove that the reduction occurs at a specific site in the cell.

The static images of ^{62}Cu-PTSM obtained from the dynamic data 2 to 10 min after injection were compared with rCBF PET images. During this period, the retention of ^{62}Cu-PTSM in the brain was almost stable, and the E · F values of ^{62}Cu-PTSM correlated relatively well with those of rCBF PET images. However, intersubject variation was also observed in this correlation. After the correction of the net extraction in each subject, ^{62}Cu-PTSM showed an excellent linear correlation with rCBF. Although ^{62}Cu-PTSM showed a slight underestimation in the high-flow range, it was not as severe as that with ^{99m}Tc-HMPAO (*19*). To clarify the kinetic properties of ^{62}Cu-PTSM, more complicated analysis using a compartment model may be needed.

Although the present study demonstrated some difficulty in quantitation of rCBF using ^{62}Cu-PTSM and a simple microsphere model, the relative distribution of ^{62}Cu-PTSM was correlated well with the rCBF obtained by ^{15}O-water PET, indicating that ^{62}Cu-PTSM can be used as a cerebral perfusion tracer for clinical PET studies without an in-house cyclotron.

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