A Comparative Study of Simple Methods to Measure Regional Cerebral Blood Flow Using Iodine-123-IMP SPECT

Masaki Ohkubo, Ikuo Odano and Makoto Takahashi

Department of Radiological Technology, College of Biomedical Technology, Niigata University, Niigata; Department of Radiology and Department of Psychiatry, Niigata University School of Medicine, Niigata, Japan

The aim of this study was to compare the accuracy and reliability of simple methods of quantifying regional cerebral blood flow (rCBF) with ^{123}I-labeled *N*-isopropyl-*p*-iodoamphetamine (IMP) and SPECT and to determine which method was best. **Methods:** Four methods were examined: (a) the microsphere method with continuous withdrawal of arterial blood, which was based on a microsphere model using the SPECT image obtained 5 min after tracer injection, (b) the microsphere method with one-point sampling, which was the same as the first method except that one-point sampling was used instead of continuous withdrawal, (c) the modified microsphere method with one-point sampling, which was the same as the second method except that a later SPECT image (30-min postinjection) with correction was used and (d) a table look-up method based on a two-compartment model with one-point arterial blood sampling and two SPECT scans obtained 40- and 180-min postinjection. The accuracy of these methods was validated by comparing the rCBF values with those obtained by nonlinear least squares fitting analysis based on the two-compartment model in 15 subjects. **Results:** Regional cerebral blood flow values obtained by the first method correlated most closely with those obtained by nonlinear least squares fitting analysis (error, 6.8%). The second method estimated rCBF with a mean error of 10.4%. The third method estimated rCBF with a mean error of 13.1%, even though it tended to slightly overestimate rCBF. The fourth method was inclined to underestimate rCBF with a mean error of 17.1%, and it greatly overestimated regional distribution volume. **Conclusion:** The first method was the most accurate and reliable. For less invasiveness, the first method should be combined with one-point sampling instead of continuous withdrawal, which was used in the second method. When using a delayed SPECT image with a conventional SPECT scanner, the third method was considered to be superior to the fourth method.

Key Words: iodine-123-IMP; regional cerebral blood flow; SPECT; microsphere model; two-compartment model

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Iodine-123-labeled *N*-isopropyl-*p*-iodoamphetamine (IMP) (*1,2*) has been used as a tracer for cerebral perfusion with SPECT. Because it has the advantages of high first-pass extraction and subsequent retention in the brain, it has been useful in many reports on the quantitative measurement of regional cerebral blood flow (rCBF) (*3–18*). Among these, the simple method based on the microsphere model (*3–6*) has been used most commonly and is considered to be clinically accurate (*10,15–18*). On the other hand, Iida et al. (*13*) recently reported a simple method based on a two-compartment model (influx: K_1, outflux: k_2), the table look-up method. The two-compartment model is more appropriate for the analysis of IMP kinetics in the brain than the microsphere model because it includes the washout (clearance) rate constant (k_2) from brain tissue to blood (*9–11,15,19*). However, when the two-compartment model is applied to a simple method for rCBF measurement, some standardization must be performed, e.g., using a standardized arterial input curve (standard input function) in the table look-up method. As standardization inevitably leads to some error, the method needs to be validated and compared for accuracy with other methods, especially that based on the microsphere model.

The aim of this study was to compare the accuracy and reliability of four simple methods, three of which are based on the microsphere model and a fourth on the table look-up method, and to determine which one is most effective. We validated the accuracy of these methods by comparing them with an independent technique, nonlinear least squares fitting (NLLSF) analysis based on the two-compartment model (*9–15*), combined with dynamic SPECT scans and sequential arterial blood sampling.

MATERIALS AND METHODS

Subjects

We examined 15 subjects: three normal volunteers (ages 27, 32 and 35 yr, all men), seven patients with cerebrovascular disease (age range 53–73 yr, 5 men, 2 women) and five patients with degenerative disease (age range 56–75 yr, 4 men, 1 woman). These subjects underwent dynamic SPECT scanning with frequent arterial sampling after the injection of IMP. No subject had cardiac or pulmonary disease. Informed consent was obtained from each subject after thorough explanation.

Four Methods of Regional Cerebral Blood Flow Measurement

We examined the following four methods of rCBF measurement. The schematic protocol is shown in Figure 1.

Method 1: Microsphere Method with Continuous Withdrawal. Values of rCBF (ml/g/min) are calculated by the following equation based on the microsphere model (*3*):

$$\mathrm{rCBF} = \frac{C_b(t)}{\int_0^t C_a(\tau)\, d\tau}, \qquad \text{Eq. 1}$$

where $C_a(t)$ and $C_b(t)$ are the decay-corrected radioactivity concentration in arterial blood (μCi/ml) and brain tissue (μCi/g), respectively. In this study, the time (t) was chosen to be 5 min after the injection of IMP (*10,15*). Therefore, the terms of the numerator and denominator in Equation 1 were obtained by performing SPECT scan at 5 min of scanning and continuous withdrawal of arterial blood for 5 min postinjection, respectively. Although no real

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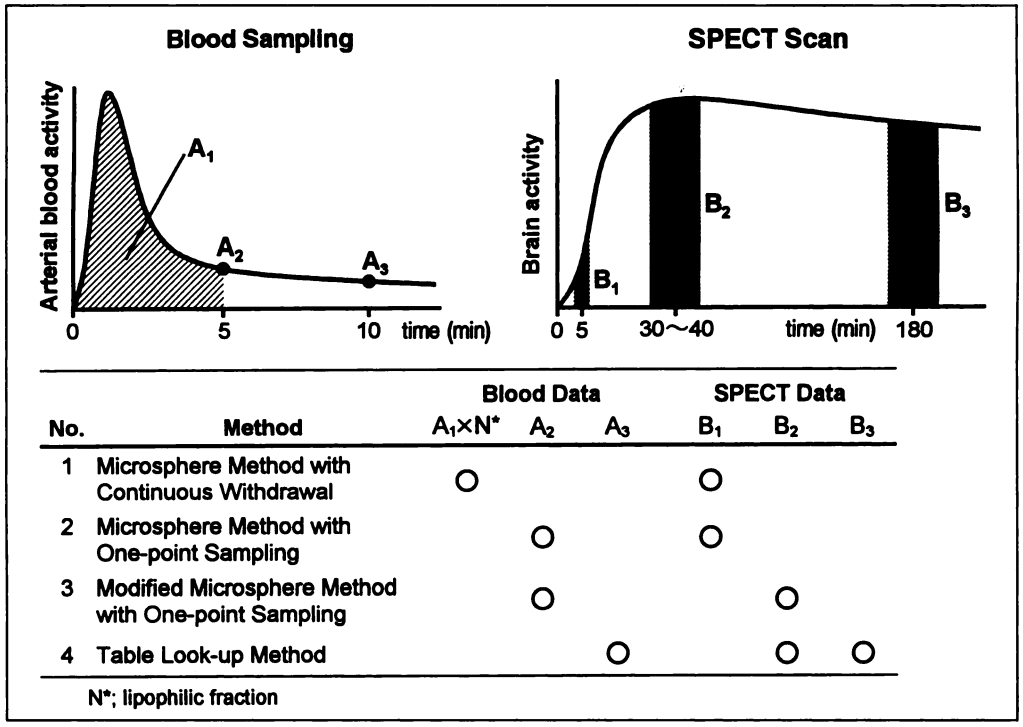
For correspondence or reprints contact: Masaki Ohkubo, Dept. of Radiological Technology, College of Biomedical Technology, Niigata University, 2-746 Asahimachi-dohri, Niigata 951, Japan.



No.	Method	Blood Data $A_1 \times N^*$	Blood Data A_2	Blood Data A_3	SPECT Data B_1	SPECT Data B_2	SPECT Data B_3
1	Microsphere Method with Continuous Withdrawal	O			O		
2	Microsphere Method with One-point Sampling		O		O		
3	Modified Microsphere Method with One-point Sampling		O			O	
4	Table Look-up Method			O		O	O

N*; lipophilic fraction

FIGURE 1. Schematic protocol of four methods used for rCBF measurement (upper), and the data required for each method (lower).

microspheres were used, this method is called the "microsphere method with continuous withdrawal" in this article.

Method 2: Microsphere Method with One-Point Sampling. Although this method is based on the same microsphere model as in Equation 1, the integral term of the denominator [integral of $C_a(t)$] is obtained by one-point sampling (*7,8*) instead of continuous withdrawal of arterial blood. We previously reported this method, in which the integral of $C_a(t)$ is estimated by using a regression curve from a small arterial sample obtained at one time point after tracer injection, without measurement of the lipophilic fraction for the blood sample (*7,8*). We then studied more subjects (n = 25) and modified the regression curve as in Figure 2 (used in this study), in which the optimum sampling time was determined to be 5-min postinjection rather than the 6 min in the previous study. The mean error of the integral of $C_a(t)$, as estimated using this regression curve, was 9.3% (25 subjects). This method is referred to here as the microsphere method with one-point sampling.

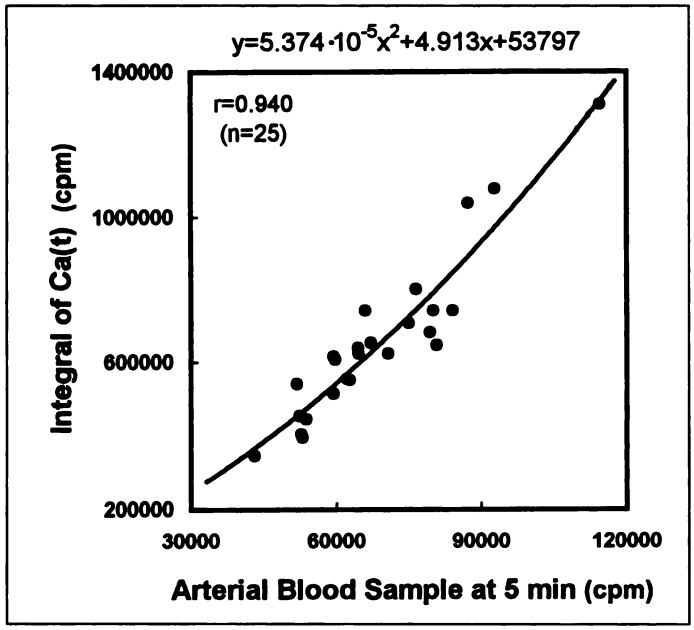


FIGURE 2. Relationship between the integral of $C_a(t)$ and one arterial blood sample obtained at 5 min after tracer injection. By using the regression curve, the integral of $C_a(t)$ can be estimated from a small arterial sample with a mean error of 9.3%.

Method 3: Modified Microsphere Method with One-Point Sampling. With a conventional SPECT scanner commonly used, it is difficult to obtain enough SPECT data 5 min after tracer injection with a short scan duration because of the poor activity in brain tissue. A later SPECT scan with a long scan duration is thus required. Using the later image corrected with the ratio of alteration of entire brain activity [C(t)], the values of rCBF are calculated by the following equation based on the microsphere model (*3,5,6,15*):

$$rCBF = \frac{C_b(T) \times \dfrac{C(t)}{C(T)}}{\displaystyle\int_0^t C_a(\tau)\, d\tau}, \qquad \text{Eq. 2}$$

where C(t) is the decay-corrected radioactivity concentration in the entire brain (μCi/g). In this study, the SPECT scanning time chosen was 30 min (T = 30 min), and the time of microsphere model analysis was 5 min (t = 5 min). In addition, the integral of $C_a(t)$ in Equation 2 was obtained by one-point sampling as mentioned above. We call this method the "modified microsphere method with one-point sampling."

Method 4: Table Look-up Method. This method requires two SPECT scans, at 40 and 180 min, and one arterial blood sample 10 min after tracer injection (*13*). Using a standardized arterial input function calibrated with the blood sample, rCBF and regional distribution volume ($V_d = K_1/k_2$) were calculated based on the two-compartment model using the table look-up procedure. We used the original method (*13*) without any modification.

Dynamic IMP SPECT

Dynamic SPECT Scan. A dose of 222 MBq of IMP was injected into a cubital vein over 1 min. After the injection, sequential SPECT scans were obtained at a scan duration of 5 min from 2.5 to 60 min, and an additional SPECT scan was performed at 180 min for the table look-up method. At the same time, sequential arterial blood sampling was simultaneously performed through a catheter inserted into the radial artery of the side opposite the injection. Sampling was performed every 15 sec from 0 to 2 min, every 30 sec from 2 to 5 min, every 1 min from 5 to 10 min and then at 12, 14, 16, 20, 25, 30, 40, 50 and 60 min after tracer injection. Whole-blood radioactivity concentrations and their octanol extraction fractions (lipophilic fraction) were measured for all blood samples (*3–6*). The arterial input function was obtained by multiplying the whole-blood radioactivity concentration by the octanol extraction fraction for each sample (*10–15*).

SPECT Scanners. We used two types of SPECT scanners, a ring-type model equipped with a high-resolution collimator, used on 10 of 15 subjects, and a three-head rotating gamma camera equipped with a high-resolution fan-beam collimator, used on five subjects. SPECT images were reconstructed in 128 × 128 matrices using a filtered backprojection algorithm with a ramp and Butterworth filter. The effective spatial resolution was 8.7-mm FWHM at the center of the transaxial field of view in the Headtome SET-050 and 8.0 mm in the GCA-9300A/HG. Attenuation correction was done numerically by assuming an elliptical brain outline (*20*). Each SPECT transaxial slice was obtained parallel to the orbito-meatal line, and the slice thickness was 5 mm. In the GCA-9300A, scatter correction was performed using the triple energy-window method (*21*).

Cross-Calibration. To calibrate the sensitivity of the SPECT scanner against a well-scintillation counter system, a cylindrical uniform phantom (16 cm in inner diameter and 15 cm high) was used. The phantom was composed of water and 11 samples of different concentrations of IMP, and a SPECT scan was taken. The samples were taken from the phantom after the SPECT scan, and the radioactivity of each was measured using the well-scintillation counter. The activity of the SPECT image was linearly related to the activity concentration measured with the well-scintillation counter, and its linear regression line was used as the cross-calibration. This procedure was performed for each SPECT scanner.

Regional Cerebral Blood Flow Measurements. With the four abovementioned methods, rCBF was calculated by using the data derived from the dynamic SPECT scans, $C_b(t)$, and the arterial input function, $C_a(t)$. In the modified microsphere method with one-point sampling, overall brain activity, C(t) in Equation 2, was derived from the total counts of all ring-type detectors (20 cm ϕ × 10 cm) for the Headtome SET-050 SPECT scanner or total counts in regions of interest (ROIs) drawn around the entire brain on all SPECT images for the GCA-9300A/HG SPECT scanner. Regional cerebral blood flow values determined by these methods were compared with those obtained by NLLSF analysis (*22*) based on the two-compartment model (*9–15*). The kinetic model of IMP has been approximated by the two-compartment model (*9,11,13*). When measuring rCBF, we placed irregularly shaped ROIs on the SPECT images. Three ROIs were placed in the frontal cortex of each hemisphere, two in the temporal cortex, two in the occipital cortex, one in the parietal cortex, one in the centrum semiovale and one in the basal ganglia. On each slice, 15 and 20 mm above the orbito-meatal line, two ROIs were placed in each of the bilateral cerebellar cortices and brain stem. 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.

RESULTS

Regional cerebral blood flow values calculated by the four methods were compared with those obtained by NLLSF analysis (Fig. 3) in 375 ROIs of 15 subjects. Regional cerebral blood flow values obtained by the microsphere method with continuous withdrawal showed the best correlation (r = 0.946) with those obtained by NLLSF analysis, followed by those of the microsphere method with one-point sampling (r = 0.897), the modified microsphere method with one-point sampling (r = 0.893) and the table look-up method (r = 0.756). Both methods A and B in Figure 3 were found to estimate rCBF with little bias: the mean errors of estimated rCBF were 6.8% and 10.4%, respectively. The modified microsphere method with one-point sampling estimated rCBF with a mean error of 13.1%, even though it tended to slightly overestimate rCBF (Fig. 3C). The table look-up method was inclined to underestimate rCBF, with a mean error of 17.1% (Fig. 3D).

Figure 4 shows a comparison of V_d values calculated by the table look-up method with those obtained by NLLSF analysis using the same data as in Figure 3. The table look-up method greatly overestimated V_d (mean ± s.d.: 28.0 ± 7.0 ml/g in NLLSF analysis, 42.9 ± 8.4 ml/g in the table look-up method in all ROIs) and showed a poor correlation (r = 0.441).

DISCUSSION

This study showed that the most accurate and reliable method of rCBF measurement with IMP SPECT is the microsphere method with continuous withdrawal (method 1), which uses the SPECT image obtained several minutes after tracer injection. For a less invasive procedure, the microsphere method should be combined with one-point sampling instead of continuous withdrawal (method 2). When using the later SPECT image obtained with a conventional SPECT scanner, the modified microsphere method with one-point sampling (method 3) is superior to the table look-up method (method 4) because method 3 was found to be more accurate than method 4. In addition, method 4 has the disadvantage of requiring the SPECT scan at 180 min postinjection, and the values of V_d obtained by this method were greatly overestimated. It should also be noted that methods 3 and 4 tended to slightly overestimate and underestimate rCBF, respectively.

Methods Based on the Microsphere Model

Although rCBF measurement by the microsphere method is considered to underestimate rCBF because of the washout of IMP from brain (*10,11,15*), for up to several minutes after tracer injection, it provides an accurate estimate of rCBF (*10,15*). In this study as well, when the 5-min postinjection SPECT image was used, rCBF values calculated by the microsphere method with continuous withdrawal (method 1) were in good agreement with those obtained by NLLSF analysis based on the two-compartment model (Fig. 3A). Although there is no clear physiological justification for the use of the two-compartment model for describing IMP kinetics in the brain, its validity has been suggested (*9,11,13*). The most accurate and reliable method of rCBF measurement with IMP SPECT, as well as NLLSF analysis, was determined to be method 1.

Method 1 is, however, invasive and laborious. One-point sampling (*7,8*) was, therefore, developed instead of continuous withdrawal. This method estimates the integral of $C_a(t)$ in Equation 1 from a small arterial sample obtained 5 min postinjection, without the measurement of the lipophilic fraction of the sample. The mean error of the integral of $C_a(t)$, as estimated by this method in 25 subjects, was 9.3% (Fig. 2), thus

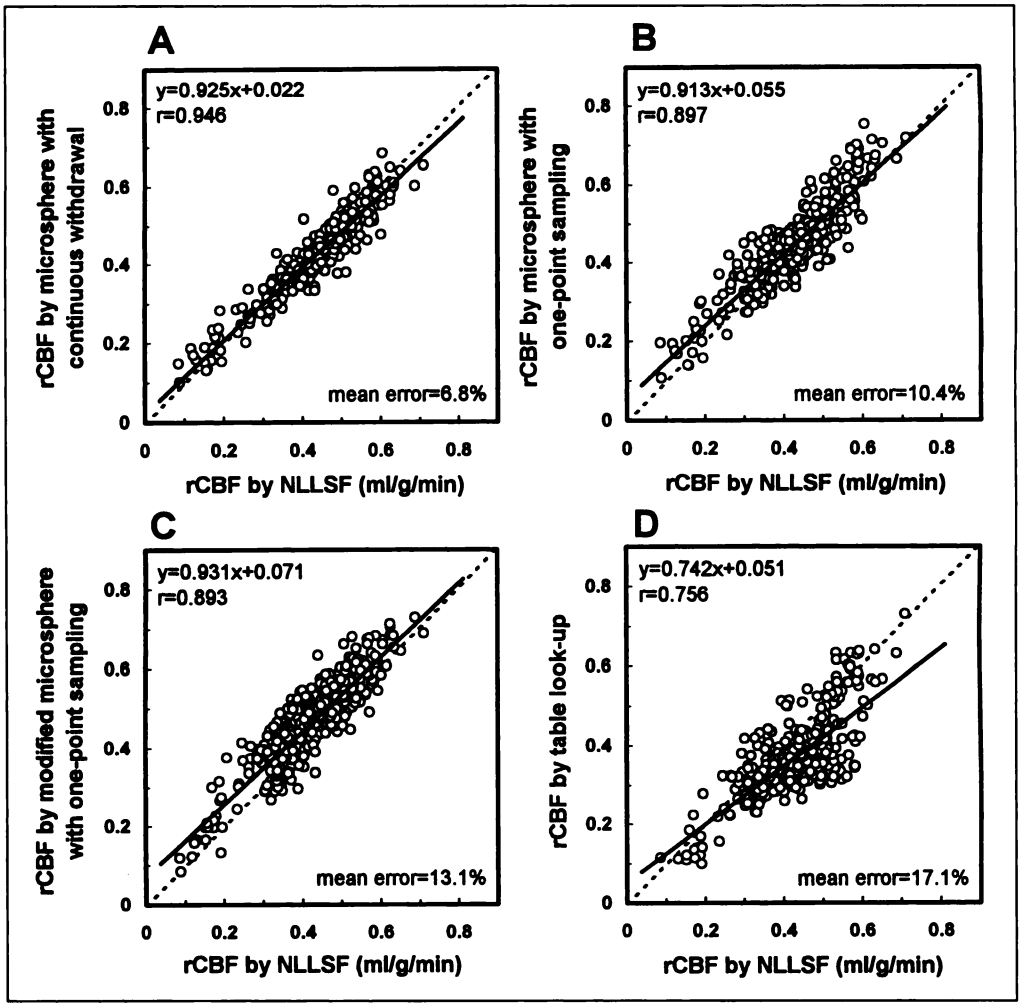


FIGURE 3. Comparison of rCBF values calculated by four methods with those obtained by NLLSF analysis in 375 ROIs of 15 subjects. The microsphere method with continuous withdrawal showed the best correlation (A), followed by the microsphere method with one-point sampling (B), the modified microsphere method with one-point sampling (C) and the table look-up method (D).

suggesting its validity. Regional cerebral blood flow values calculated by the microsphere method with one-point sampling (method 2) were significantly correlated with those obtained by NLLSF analysis (Fig. 3B) with an estimation error of 10.3%. Therefore, we consider method 2 to be both accurate and less invasive. When a high performance SPECT scanner is being used, this method should be chosen for clinical use.

Methods 1 and 2 require performing the SPECT scan several minutes after tracer injection. However, when using a conventional SPECT scanner, a later SPECT scan with a long scan duration is required. For determining rCBF, the later image is corrected to represent activity several minutes postinjection with the ratio of alteration of measured entire brain activity. Kuhl et al. (*3*) reported the basic procedure of this correction, and Matsuda et al. (*5*) applied it to use with a conventional rotating gamma camera, as indicated in Equation 2. Although this method has not been clearly validated, it has been generally used (*16–18*). In this study, rCBF values calculated by the modified microsphere method with one-point sampling (method 3) were significantly correlated with those obtained by NLLSF analysis (Fig. 3C) with an estimation error of 13.1%. We conclude that method 3 is clinically accurate, convenient and less invasive. However, this method tended to slightly overestimate rCBF. Correction of the SPECT image with overall brain activity must be considered among the reasons for this (*15,23*).

Table Look-up Method

The table look-up method (method 4) makes it easy to measure rCBF based on the two-compartment model (*13*) but has the disadvantage of requiring the SPECT scan 180 min postinjection. The precise superimposition of ROIs on two SPECT images scanned at 40 and 180 min is required again. However, the value of V_d is estimated in this method. V_d is considered to be an indicator of IMP retention and is suggested to be related with tissue viability in the brain (*16,24*). It is reported that rCBF values calculated by method 4 are significantly correlated with those obtained by NLLSF analysis and the ^{15}O-water PET method (*13*). In this study as well, rCBF values calculated by method 4 were significantly correlated with those obtained by NLLSF analysis (Fig. 3D). However, this method was found to underestimate rCBF and to show larger estimation error than other methods based on the microsphere model. Values of V_d obtained by this method were remarkably overestimated compared with those obtained by NLLSF analysis (Fig. 3) and those in other studies (*10–12*).

For the analysis of IMP kinetics in the brain, the two-compartment model is more appropriate than the microsphere model (*9–11,15,19*); however, method 4 uses a standardized arterial input function with calibration instead of determining the input function of each subject individually. The error related to using the standard input function must be considered (*25*),

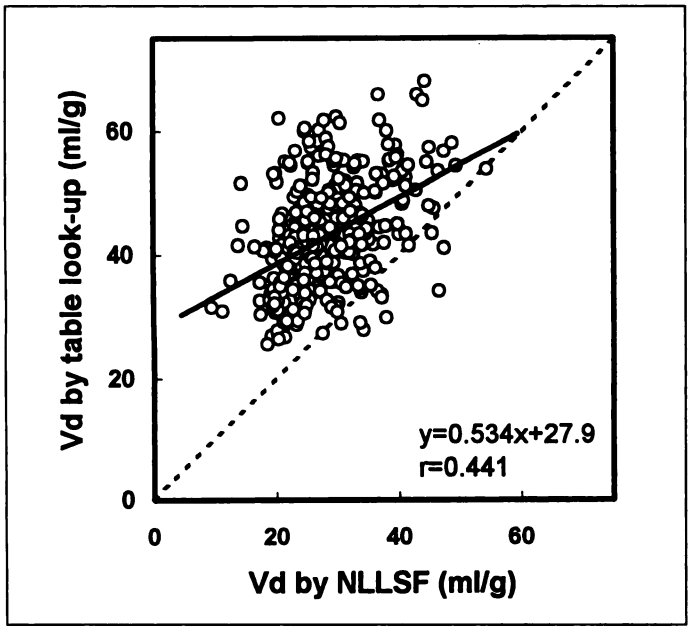


FIGURE 4. Comparison of V_d values calculated by the table look-up method with those obtained by NLLSF analysis in 375 ROIs of 15 subjects.

and it may be one reason for the underestimation of rCBF and overestimation of V_d found in this study. However, a simplified table look-up method has been reported (*14*), and this method is also considered to include the error related to using the standard input function.

Better Conventional Method

When a conventional SPECT scanner with a long scan duration is used, the modified microsphere method with one-point sampling (method 3) is considered better for clinical use than the table look-up method (method 4).

Whereas method 4 uses a standard input function, methods using the microsphere model require a value of the integral of $C_a(t)$ in Equation 1. In other words, they do not require $C_a(t)$ as a function. As the value of the integral of $C_a(t)$ is measured for each subject individually, methods using the microsphere model are considered not to depend on an input function, unlike method 4. This is probably one reason that the microsphere model generally has been used with confidence, even though it is the inferior model. The one-point sampling method also is expected not to be susceptible to an input function because of the use of the regression curve, as in Figure 2, without a standard input function. This study indicated that method 3 was more accurate than method 4. In addition, because method 4 has the disadvantage of requiring the SPECT scan 180 min postinjection, we conclude that method 3 is better.

CONCLUSION

This study demonstrated that the most accurate and reliable method of rCBF measurement with IMP SPECT is the microsphere method with continuous withdrawal, followed by the microsphere method with one-point sampling, the modified microsphere method with one-point sampling and the table look-up method. Our results are useful for choosing the method of rCBF measurement in routine clinical studies.

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