

A comparative study of simple methods to quantify cerebral blood flow with acetazolamide challenge by using iodine-123-IMP SPECT with one-point arterial sampling

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The aim of this study was to compare the accuracy of simplified methods for quantifying rCBF with acetazolamide challenge by using ^{123}I -N-isopropyl-p-iodoamphetamine (IMP) and SPECT with one-point arterial sampling. After acetazolamide administration we quantified rCBF in 12 subjects by the following three methods: (a) the modified microsphere method, (b) the IMP-autoradiographic (ARG) method based on a two-compartment one-parameter model, and (c) the simplified method based on a two-compartment two-parameter model (functional IMP method). The accuracy of these methods was validated by comparing rCBF values with those obtained by the standard method: the super-early microsphere method with continuous withdrawal of arterial blood. On analyzing rCBF in each flow range (0–0.25, 0.25–0.5, 0.5–0.75 and more than 0.75 ml/g/min), rCBF values obtained by both methods (a) and (c) showed significant correlations ($p < 0.01$) with those obtained by the standard method in every range, but rCBF values obtained by method (b) did not significantly correlated in the high flow range (0.5–0.75 and more than 0.75 ml/g/min). Method (c) was found to be the most accurate, even though it needs two serial SPECT scans. When requiring one SPECT scan, method (a) was considered to be superior to method (b) because of its accuracy, especially in high flow regions loaded with acetazolamide.

Key words: iodine-123-IMP, regional cerebral blood flow, SPECT, acetazolamide, compartment analysis

INTRODUCTION

IODINE-123-LABELED N-isopropyl-p-iodoamphetamine (IMP)¹ has been used to map brain perfusion with SPECT and is useful in quantitative measurement of regional cerebral blood flow (rCBF).^{2–7} Recently three types of less invasive and simplified methods for quantifying rCBF have been proposed,^{8–14} which techniques do not require dynamic SPECT scanning, continuous withdrawing or frequent arterial sampling, and separating lipophilic

fractions of the blood samples. The first is the modified microsphere method with one-point arterial sampling instead of continuous withdrawing.^{8–10} This method requires a static SPECT image, which image is corrected to represent activity several minutes after IMP infusion by means of the ratio of alteration of measured entire brain activity. The second is the IMP-autoradiographic (ARG) method,^{11,12} which was based on a two-compartment one-parameter model (influx: K_1 , outflux: k_2 , fixed K_1/k_2) with one-point sampling and a static SPECT scan. The third is a more functional method (functional IMP method)^{13,14} of quantifying not only rCBF but also the partition coefficient ($\lambda = K_1/k_2$) which is suggested to be related to tissue viability in the brain.^{15,16} This method is based on a two-compartment model (K_1, k_2) with one-point sampling and two serial SPECT scans.

The validity of the above three methods has been

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evaluated in SPECT studies at rest,⁸⁻¹⁴ but not in an acetazolamide test or any other physiological or chemical test. Acetazolamide, a carbonic anhydrase inhibitor, is used commonly as a cerebral vasodilator drug in SPECT studies. Although sequential measurements of pre- and post-acetazolamide rCBF in a single procedure were reported,^{17,18} these require arterial catheterizing and dynamic or super-early SPECT scanning. More simple methods should be applied also to the acetazolamide test.

The aim of this study was to compare the accuracy and reliability of the three simple methods mentioned above with acetazolamide challenge, and to determine which one is the most effective. The reference for comparison was the microsphere method with continuous withdrawal of arterial blood and using the super-early SPECT image after IMP infusion.^{2,3} Since the acetazolamide effect is time dependent,¹⁹⁻²¹ the microsphere method is considered to be more accurate for detecting its effect because of the short time of measurement.

MATERIALS AND METHODS

Subjects

We examined 12 patients: ten patients with cerebrovascular disease (age range 29-76 yr, 5 men and 5 women), one (a 38-yr-old man) with mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) and one (a 40-yr-old man) with neuro-Behcet's disease. These patients underwent IMP SPECT scanning with arterial sampling after the intravenous administration of acetazolamide. No patient had cardiac or pulmonary disease or was a smoker. Informed consent was obtained from each patient after thorough explanation.

Three Methods of rCBF Measurement

Since IMP behaves like a microsphere soon after infusion, the method for quantifying rCBF based on a microsphere model is valid,^{2,3} and requires SPECT scanning for the first several minutes and continuous withdrawal of arterial blood. This "microsphere method" calculates rCBF (ml/g/min) by means of the following equation:

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

where $C_a(t)$ and $C_b(t)$ are the decay-corrected radioactivity concentration in arterial blood ($\mu\text{Ci/ml}$) and brain tissue ($\mu\text{Ci/g}$), respectively. In this study, the chosen time (t) was to be 5 min after the injection of IMP, which time had been validated.^{6,22} We chose this method as the standard for comparing the following three methods.

Method 1: Modified Microsphere Method. With a conventional SPECT scanner commonly used, it is difficult to obtain enough SPECT data several minutes (time t) after tracer injection with a short scan duration because of the poor activity in brain tissue. A later SPECT scan (time T) with relatively long scan duration is therefore

required. By using the later image ($C_b(T)$) corrected with the ratio of alteration of entire brain activity ($C(t)/C(T)$), rCBF values are calculated by means of the following equation:^{2,4,10}

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

where $C(t)$ is the decay-corrected radioactivity concentration in entire brain ($\mu\text{Ci/g}$). $C(t)$ is measured, generally by using the planar image count, accurately even several minutes postinjection because of the sufficient activity in the entire brain. With this modification, the microsphere method became able to be used with a current head-rotating camera.^{15,23} In this study, the static SPECT scan time chosen was to be 30 min of scanning, $T = 30$ min, and the time for microsphere model analysis 5 min, $t = 5$ min.¹⁰

In addition, the integral term of the denominator (integral of $C_a(t)$) is obtained by a one-point sampling method⁸⁻¹⁰ instead of continuous withdrawal of arterial blood. With this technique, the integral of $C_a(t)$ is estimated by means of a regression curve from a single arterial sample obtained at one time point (5 min) after tracer injection, without measurement of the lipophilic fraction for the blood sample. We call this method the "modified microsphere method" in this study.

Method 2: Two-Compartment One-Parameter Model Method (ARG Method). Iida et al. proposed a simple method called the table look-up method,²⁴ based on a two-compartment two-parameter model (K_1, k_2). This method requires two SPECT scans, at 40 and 180 min, and one-point arterial blood sampling after tracer injection. By using a standardized arterial input calibrated with the blood sample, rCBF and the partition coefficient ($\lambda = K_1/k_2$) were calculated by means of the table look-up procedure. The method has disadvantages in terms of the delayed scan at 180 min,¹⁴ and is considered not able to be applied to acetazolamide challenge because the acetazolamide effect is time dependent. A simplified table look-up method, the autoradiographic (ARG) method, has also been reported.^{11,12} The ARG method is theoretically the same as the table look-up method except for assuming a fixed λ value, that is, it is based on a two-compartment one-parameter model (K_1). Consequently the delayed SPECT scan is not required, and the ARG method is employed in the acetazolamide test. In this study, we utilized the original ARG method,¹¹ in which the time of SPECT scanning and that of arterial sampling were to be 30 min and 10 min postinjection, respectively, as proposed by Iida et al.^{11,12} The fixed value for λ used in the ARG method is 43 ml/g which was the mean value for 15 patients measured at rest by the table look-up method in our previous study.¹⁰

Method 3: Two-Compartment Two-Parameter Model Method (functional IMP method). This method, recently proposed,^{13,14} quantifies both rCBF and the functional

parameter of the partition coefficient (λ) based on the two-compartment model, and we call this the “functional IMP method” in this paper. Briefly, the functional IMP method requires one-point arterial sampling and two serial SPECT scans (30 min and 60 min) in the early phase without the delayed SPECT scan. Although this method was based on the two-compartment model, as used in the table look-up method, the mathematical functions for calculating rCBF and λ originated in a new theoretical approach as follows,^{13,14}

$$\begin{aligned} \text{rCBF} &= \frac{C_b(30 \text{ min})}{\int_0^{5 \text{ min}} C_a(t) dt} \cdot \frac{C_b(5 \text{ min}) + k_2 \int_0^{5 \text{ min}} C_b(t) dt}{C_b(30 \text{ min})} \\ &= \frac{C_b(30 \text{ min})}{\int_0^{5 \text{ min}} C_a(t) dt} \cdot \Phi \left(\frac{C_b(30 \text{ min})}{C_b(60 \text{ min})} \right) \quad \text{Eq. 3} \end{aligned}$$

$$\begin{aligned} \lambda &= \frac{C_b(30 \text{ min})}{\int_0^{5 \text{ min}} C_a(t) dt} \cdot \frac{C_b(5 \text{ min}) + k_2 \int_0^{5 \text{ min}} C_b(t) dt}{k_2 C_b(30 \text{ min})} \\ &= \frac{C_b(30 \text{ min})}{\int_0^{5 \text{ min}} C_a(t) dt} \cdot \Gamma \left(\frac{C_b(30 \text{ min})}{C_b(60 \text{ min})} \right) \quad \text{Eq. 4} \end{aligned}$$

where the functions Φ and Γ in Equations 3 and 4 in $C_b(30 \text{ min})/C_b(60 \text{ min})$ variables are standard functions obtained by analyzing the individual function computed from the $C_a(t)$ for many subjects. By using these functions, values for the second term in Equations 3 and 4 are calculated by means of two SPECT scans without any $C_a(t)$ data. In addition, the integral of $C_a(t)$ in Equations 3 and 4 is

obtained by using the one-point sampling method⁸⁻¹⁰ mentioned above, which does not require the standardized arterial input with calibration as used in the table look-up method. Then rCBF and λ are quantified by means of two serial SPECT scans with single arterial sampling. In this study, we used the original method^{13,14} without any modification.

SPECT Procedure

At 10 min after the intravenous administration of 1 g/60 kg acetazolamide for 20 seconds, a dose of 222 MBq of IMP (Nihon Medi-Physics, Takarazuka, Japan) was injected via a cubital vein in 1 min. After the IMP injection, SPECT scans were performed at 5 min, 30 min and 60 min of mid scan time, with a scan duration of 5 min, 20 min and 20 min, respectively. The continuous withdrawal of arterial blood was performed from 0 to 5 min through a catheter inserted into the radial artery on the side opposite the IMP injection, after which one-point arterial blood was withdrawn at 5 min and 10 min. The integral of $C_a(t)$ in Equation 1 was obtained by multiplying the whole-blood radioactivity concentration by the octanol extraction fraction (lipophilic fraction)²⁻⁴ for the blood sample continuously withdrawn for 5 min. The one-point blood samples obtained at 5 min and 10 min were used for methods 1-3 without the octanol extraction.

SPECT Scanners. We used a three-head rotating gamma camera (GCA-9300A/HG [Toshiba Corp., Tokyo, Japan]) equipped with a high-resolution fan-beam collimator. SPECT images were reconstructed in 128×128 matrices by using a filtered back-projection algorithm with a Ramp and Butterworth filter. The effective spatial resolution was 8.0 mm full width at half maximum

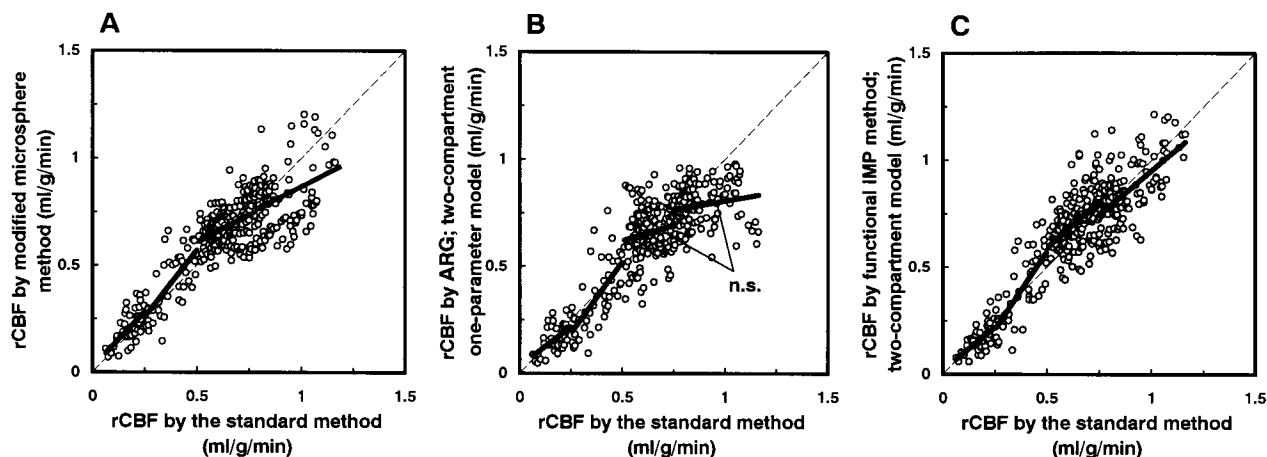


Fig. 1 Comparison of rCBF values calculated by three methods with those obtained by the standard method in 384 ROIs of 12 patients. On analyzing rCBF in each flow range (0–0.25 ml/g/min, 0.25–0.5 ml/g/min, 0.5–0.75 ml/g/min and more than 0.75 ml/g/min), rCBF values obtained by both the modified microsphere method (A) and the functional IMP method (C) showed significant correlations ($p < 0.01$) with those obtained by the standard method in every range, but rCBF values obtained by the ARG method (B) did not significantly correlated in the high flow range (0.5–0.75 ml/g/min and more than 0.75 ml/g/min).

(FWHM) at the center of the transaxial field of view (FOV). Both absorption correction by Chang's method and scatter correction by the triple energy window method could be performed.²⁵ Each SPECT transaxial slice was obtained parallel to the orbito-meatal (OM) line, and the slice thickness was 5 mm.

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 their radioactivity measured in a 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 in cross-calibration.

rCBF measurements. rCBF values determined by the three above-mentioned methods were compared with those obtained by the microsphere method as indicated in Equation 1. In the modified microsphere method, overall entire brain activity, $C(t)$ in Equation 2, was derived from the total counts in regions of interest (ROIs) drawn around the entire brain on all SPECT images. When measuring rCBF, we placed irregularly shaped ROIs in the frontal, temporal, occipital and parietal cortices, basal ganglia, thalamus, centrum semiovale and cerebellum (total 25–35 ROIs). These regions were anatomically identified by referring to X-ray computed tomography (X-CT) images that were obtained on the same day as the IMP SPECT studies. Through the comparative study of all methods, we did not take up the data in two ROIs out of a total of 386 ROIs for all patients. From these two ROIs the ARG method could not provide rCBF values.

RESULTS

Figure 1 shows a comparison of rCBF values calculated by three methods with those obtained by the standard method. rCBF values obtained by the functional IMP method were the most closely correlated with those obtained by the standard method ($r = 0.892$), followed by those of the modified microsphere method ($r = 0.864$) and the ARG method ($r = 0.848$). On analyzing rCBF in each flow range (0–0.25 ml/g/min, 0.25–0.5 ml/g/min, 0.5–0.75 ml/g/min and more than 0.75 ml/g/min), rCBF values obtained by both methods A and C in Figure 1 showed significant correlations ($p < 0.01$) with those obtained by the standard method in every range. Nevertheless, rCBF values obtained by the ARG method (Fig. 1B) were not significantly correlated in the high flow range (0.5–0.75 ml/g/min and more than 0.75 ml/g/min).

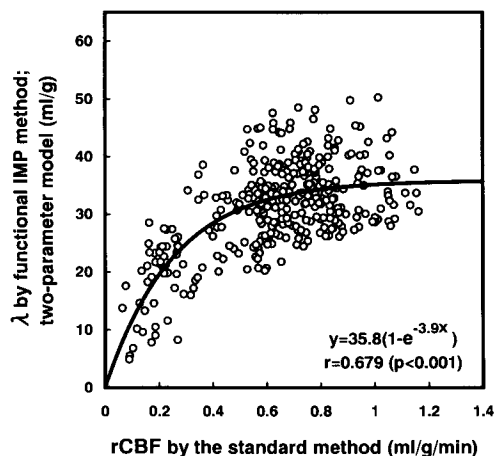


Fig. 2 The relationship between the values for λ obtained by the functional IMP method and rCBF obtained by the standard method, in which the data are the same as indicated in Figure 1.

DISCUSSION

This study showed that, in IMP SPECT studies with acetazolamide challenge, the most accurate and reliable method of rCBF measurement with one-point arterial sampling is the functional IMP method (method 3), which requires two serial SPECT scans. When one SPECT scan is performed, the modified microsphere method (method 1) is considered to be superior to the ARG method (method 2) because method 1 was found to be more accurate than method 2 especially in high flow regions of rCBF loaded with acetazolamide.

To compare the three methods, we chose the microsphere method as the standard. The acetazolamide effect is time dependent and thought to reach a maximum at 10 to 20 min after administration.^{19–21} In this study, IMP was injected at 10 min after the administration of acetazolamide, and 5 min after that, the super-early SPECT scan was performed. Therefore, using the microsphere method with the super-early image, we can measure rCBF greatly affected by the acetazolamide. In IMP SPECT studies with acetazolamide challenge, the microsphere method is considered to be more appropriate for measuring rCBF than other methods such as the non-linear least squares fitting analysis^{5,6} or the graphical method.⁷

Previously, a one-point sampling method was proposed,^{8–10} in which the integral of arterial input is estimated by using a regression curve from small amount of arterial sample obtained 5 min after IMP infusion. This method does not require the standardized arterial input with calibration as used in the table look-up method, but has not been investigated for patients with cardiac or pulmonary disease. By applying this technique, we simplified the microsphere method (method 1)^{8–10} and furthermore proposed the functional IMP method for quantifying both rCBF and the partition coefficient (λ).

based on the two-compartment model (method 3).^{13,14} These methods have been validated in SPECT studies at rest. In this study, rCBF values calculated by both methods 1 and 3 were significantly correlated with those obtained by the standard method, suggesting the validity of the methods also with acetazolamide challenge. Taking the simplicity into account, their accuracy are considered to be satisfactory for routine clinical studies although maybe less so than those of other methods requiring more invasive and laborious procedures.²⁻⁷ Method 1 (Fig. 1A) was less accurate than method 3 (Fig. 1C), especially in the high flow range. This may be due to the correction of the SPECT image with overall brain activity as indicated in Equation 2.^{10,26} In method 3, we consider that the estimation of λ is valuable for measuring rCBF, especially in the high flow range, but the measurements of rCBF and λ might be sensitive to error in the SPECT data (statistical error) because of the short interval between two SPECT scans.

The table look-up method is a simple method for quantifying both rCBF and λ based on the two-compartment model.²⁴ The IMP-autoradiographic (ARG) method is theoretically the same as the table look-up method except that λ is assumed to be constant, therefore based on the two-compartment one-parameter model.¹¹ The ARG method is very simple because it requires only one SPECT scan without the measurement of overall brain activity as required in the modified microsphere method. The ARG method has been validated in SPECT studies at rest.^{11,12} With acetazolamide challenge in this study as well, we found significant correlation of rCBF with the ARG method and the standard method in the normal flow range, but not in the high flow range (Fig. 1B). This may be due to the errors related to using the standard arterial input,^{10,27,28} the fixed value for λ and the assumption that λ is constant. Although Iida et al. suggested the validity of these issues,^{11,12} neither the ARG nor the table look-up method has been clearly compared for accuracy with other simple methods using IMP SPECT, that is, has been warranted to be superior to other methods.

We previously performed a comparative study of simple methods,¹⁰ and showed that the table look-up method was inferior to the modified microsphere method, and, in addition, the table look-up method overestimated λ . When the ARG method is used in most institutions, the fixed value for λ is considered to be obtained beforehand by the table look-up method in each institution (or maybe derived from the literature).¹² In this study as well, the value for λ was fixed at the mean value (43 ml/g) for 15 patients in which it was measured by the table look-up method in our previous study.¹⁰ This value was almost the same as implied in the multicenter study on the table look-up method,¹² but it was more than that obtained by the accurate reference method.¹⁰ In the ARG method, the error in the fixed λ value causes an error in the estimated rCBF, especially in the high flow range,¹¹ supporting the

results shown in Figure 1B. Further studies on λ and the standard arterial input are required in IMP SPECT studies at rest, and then with acetazolamide challenge.

Although method 3 requires two serial SPECT scans, it measured rCBF most accurately in three methods and estimated λ simultaneously. Figure 2 shows the relationship between the values for λ obtained by method 3 and rCBF obtained by the standard method, in which the data are the same as indicated in Figure 1. Analyzing the correlation by exponential approximation, we found good agreement ($r = 0.679$, $p < 0.001$). The mean value for λ was 31.2 ± 7.9 ml/g. Over the range for rCBF, approximately 0.4 ml/g/min, the change in λ was minimum with great dispersion, and λ decreased as rCBF decreased. The λ is considered to be an indicator of IMP retention and it has been suggested that it is related to tissue viability in the brain.^{15,16} Because the delayed SPECT image, which is related to λ , has been generally used in clinical studies, we consider λ to have clinical significance.

When we apply the methods used in this study to the sequential measurement of pre- and post-acetazolamide rCBF, further comparative studies should be required.

CONCLUSION

In IMP SPECT studies with acetazolamide challenge, the most accurate and reliable method of rCBF measurement with one-point arterial sampling was found to be the functional IMP method, followed by the modified microsphere method and the ARG method. Our results are useful for choosing a method for quantifying rCBF with acetazolamide challenge in routine clinical studies.

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