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Error analysis of table look-up method for cerebral blood flow measurement by ^{123}I-IMP brain SPECT: Comparison with conventional microsphere model method

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While N-isopropyl-p-[^{123}I]iodoamphetamine (IMP) is commonly used as a flow tracer, significant clearance from the brain causes underestimation of CBF as compared with true CBF when conventional microsphere model analysis is applied. We previously reported a simple "table look-up" method for CBF measurement using IMP taking into account this clearance effect. The method is based on a two-compartment model, the K_1 (corresponding to CBF) and k_2 constants being obtained from a table from the ratio of the 1st SPECT (40 min) to the 2nd SPECT (180 min) counts. Arterial input data used were obtained by one point blood sampling 10 min after IMP infusion against the standard input function. In the present study, this approach was compared with conventional microsphere model analysis. For 30 subjects, the latter method entailed 8 min continuous arterial blood sampling after IMP infusion and the use of SPECT data at the end of this period, calibrated by a count ratio of 8 min/40 min planar images of whole brains. A good correlation was observed between the two methods ($r = 0.88$), but an overestimation of table look-up method CBF as compared with microsphere model CBF was observed contrary to theoretical predictions. Limitations in the estimation of SPECT data at 8 min, obtained with SPECT data at 40 min for calibration of the count ratio of 8 min/40 min whole brain planar images, might be responsible for this.

Key words: IMP, SPECT, cerebral blood flow, table look-up method

INTRODUCTION

Iodine-123 (^{123}I) labeled N-isopropyl-p-iodoamphetamine (IMP) is used as a cerebral blood flow (CBF) tracer for single photon emission computed tomography (SPECT) due to its large extraction fraction and high affinity for the brain.[1,2] But, significant clearance from the brain causes change in IMP distribution[3,4] and underestimation of CBF when a conventional microsphere model analysis[5] is applied to prolonged data acquisition.[6–9] We previously reported a "table look-up method," a new simple approach to measurement of CBF with IMP, taking into account this clearance effect.[10–12] The approach is based on a two-compartment model (influx: K_1, efflux: k_2), in which K_1 (taken to represent CBF) and k_2 are obtained from a table read with the count ratio of first SPECT scan (mid-scan time: 40 min) to second SPECT scan (mid-scan time: 180 min). Arterial input function is obtained by calibrating against the standard input function from one point arterial blood sampling at 10 min after intravenous infusion of IMP. The purpose of the present study was to compare this method with the conventional microsphere model method[13] for a major patient series.

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MATERIALS AND METHODS

Subjects

SPECT studies were performed on 30 subjects including 19 patients suffering from cerebral contusion, 3 with cerebrovascular disease, 2 with hypoxic brain, 2 with

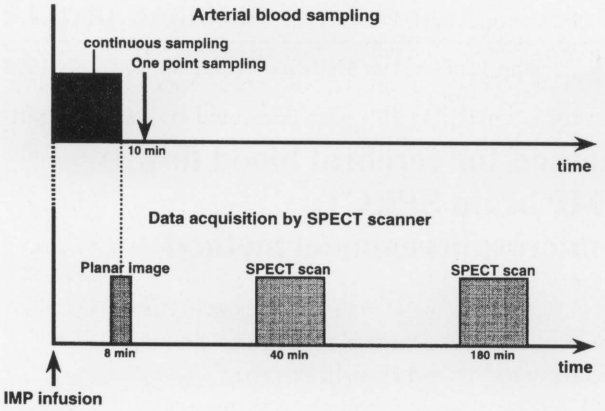

Fig. 1 The experimental protocol design shows the time schedule of scan and blood sampling. The one point arterial blood sampling from the brachial artery was performed at 10 min after IMP infusion for determination of arterial input function for the table look-up method. Continuous arterial blood sampling from the brachial artery was also performed over the 8 min after IMP infusion for the microsphere model analysis. Two SPECT scans were performed at mid-scan time of 40 and 180 min after IMP infusion for the table look-up method (40 min, 180 min) and the microsphere model analysis (40 min). Brain planar images over 50 sec were obtained at 8 min after IMP infusion for the microsphere model analysis.

carbon monoxide toxicosis and 4 normal volunteers. None of the patients had any heart or lung disease and informed consent was obtained from all subjects after proper explanation of the study being conducted.

SPECT study

Two SPECT scans were performed, at 40 min and 180 min of mid-scan time, after intravenous infusion of 222 MBq IMP lasting 1 min. Fifty sec planar brain images were obtained 8 min after IMP infusion for the conventional microsphere model analysis (Fig. 1). The SPECT scanner used was a Neurocam (Yokogawa Medical Systems Corp., Tokyo, Japan),[14] equipped with a three-head rotating gamma camera. In-plane resolution was 9 mm full width at half maximum (FWHM), and axial resolution was 10 mm FWHM. The SPECT scan protocol acquired 64 projections at 50 sec per projection with 120° rotation of the camera. Reconstruction was performed by filtered backprojection using a Butterworth filter (cutoff frequency 0.45 cycle/cm, power factor 10). Attenuation correction was made numerically by assuming the object shape to be circular or elliptical and the attenuation coefficient to be uniform. Image slices were set up parallel to the orbitomeatal (OM) line and obtained at 8 mm intervals through the whole brain.

One point arterial blood sampling from the brachial artery was performed at 10 min after IMP infusion. Radioactivity of the whole blood was measured with a well counter and was used for calibration against the standard input function to provide an arterial input function for the table look-up method.[10–12] Continuous arterial blood sampling at a constant rate from the brachial artery was also performed during the first 8 min after IMP infusion and octanol extracted radioactivity was measured for the conventional microsphere model analysis (Fig. 1).

A cross calibration scan was performed using an elliptic cylindrical uniform phantom (long axis: 19 cm, short axis: 14 cm inner diameter) for calibrating the relative sensitivities of the SPECT scanner and the well counter system.

Image analysis

Regions-of-interest in the cerebellum, pons, thalamus, putamen, centrum semiovale and cerebral cortex including frontal, temporal, parietal and occipital lobes were outlined on the 40 and 180 min SPECT images. The shape of regions-of-interest was circular with a 35 mm diameter for the cerebellum, and elliptic with a short axes of 16–25 mm and long axes of 25–50 mm for other region.

Theory

Table look-up method[10–12]:

In this method, a two-compartment model was employed in line with previous reports.[6,7,15]

$$\frac{dC_b(t)}{dt} = K_1 \cdot C_a(t) - k_2 \cdot C_b(t) \quad (1)$$

where

$C_b(t)$: concentration of radioactivity in the brain
$C_a(t)$: arterial input function
K_1: influx rate constant (ml/ml/min)
k_2: efflux rate constant (1/min)

In this study, we assumed the first-pass extraction fraction of IMP to be equal to 1[1,2,16] and therefore, K_1 equals CBF. The ratio of K_1 to k_2 is called the distribution volume of IMP in the brain (V_d (ml/ml)).

Solving Eq. 1 provides:

$$C_b(t) = K_1 \cdot C_a(t) \otimes e^{-k_2 \cdot t} \quad (2)$$

where $\otimes$ denotes the convolution integral.

For this method, two SPECT scans are performed. The model equation (Eq. 2) can therefore be expressed for each scan.

$$C_b(t_e) = K_1 \cdot C_a(t_e) \otimes e^{-k_2 \cdot t_e} \quad (3a)$$

$$C_b(t_d) = K_1 \cdot C_a(t_d) \otimes e^{-k_2 \cdot t_d} \quad (3b)$$

where t_e and t_d are mid-scan times at first and second scans, respectively. Calculating the ratio of Eq. 3a to Eq. 3b gives:

$$\frac{C_b(t_e)}{C_b(t_d)} = \frac{C_a(t_e) \otimes e^{-k_2 \cdot t_e}}{C_a(t_d) \otimes e^{-k_2 \cdot t_d}} \quad (4)$$

For a given input function, $C_a(t)$, the radioactivity ratio

of the first to second scans (the right side of Eq. 4) can be considered to tabulate as a function of k_2. For a given radioactivity ratio of first to second scans, the table look-up procedure then provides a corresponding k_2 value. By inserting this k_2 value into Eq. 3a or 3b, a K_1 value that corresponds to CBF can be calculated. The arterial input function, $C_a(t)$ is obtained by calibration against the standard input function by using the arterial blood radioactivity gained from the one point sampling.

Microsphere model method[13]:
CBF values were also calculated by microsphere model analysis as follows:

$$f = \frac{C_b}{\int_{0\ min}^{8\ min} C_a(t)dt} = \frac{C_b \cdot R}{C_a} \quad (5)$$

where

- f: CBF (ml/ml/min)
- C_b: concentration of radioactivity in the brain at 8 min after IMP infusion
- $C_a(t)$: arterial input function
- R: constant arterial blood sampling rate (ml/min)
- C_a: total octanol extracted radioactivity of the blood withdrawn over 8 min

In this study, C_b was obtained as follows:

$$C_b = \frac{C_b(Planar_8)}{C_b(Planar_{40})} \cdot C_b(SPECT_{40}) \quad (6)$$

where

- $C_b(Planar_8)$: the whole brain radioactivity of the planar image at 8 min after IMP infusion
- $C_b(Planar_{40})$: the whole brain radioactivity of the planar image at 40 min which is one of the projections of SPECT scans
- $C_b(SPECT_{40})$: the brain radioactivity concentration of the SPECT scan with the mid-scan time of 40 min after IMP infusion

Simulation of CBF correlation between the two compartment model and the microsphere model
For prediction of systematic underestimation of CBF by microsphere model analysis, a simulation of the correlation between CBF values evaluated by the two-compartment model analysis and those from microsphere model analysis was performed. CBF values from the microsphere model were calculated as follows: Firstly, the brain radioactivity curve, $C_b(t)$ was generated for a CBF range of 0 to 100 ml/100 ml/min according to the two-compartment model equation (Eq. 2) where the V_d values were 20, 30, 40 or 50. The standard input function used in the table look-up method was employed for the arterial input function, $C_a(t)$. Secondly, for each calculated $C_b(t)$, the microsphere model CBF values were calculated using $C_b(t)$ at 8 min and integrated with $C_a(t)$ for the time period [0, 8 min] (Eq. 5). The resultant microsphere model CBF values were compared with those generated by two-compartment model analysis.

Simulation of the effects of gray-white matter mixture
The limited spatial resolution of SPECT scanners causes gray-white matter mixture in regions-of-interest. The effects of gray-white matter mixing on CBF values calculated by the table look-up method were evaluated.[17] The heterogeneous tissue radioactivities at first and second SPECT scans were generated as mixtures of gray and white matter. CBF values of the gray and white matter were assumed to be 80 and 20 ml/100 ml/min, respectively. The V_d value of gray and white matter was assumed to be the same as 30, 35, 40, 45 or 50 ml/ml. The difference between true CBF values (= 80 ml/100 ml/min × gray matter fraction + 20 ml/100 ml/min × white matter fraction) and CBF values calculated by table look-up method with the generated heterogeneous tissue radioactivity were estimated where the fraction of gray matter per given region-of-interest varied from 0 to 100%. In this simulation, the arterial input function was the standard input function used for the table look-up method.

Simulation of CBF correlation between the two-compartment model and the microsphere model method in which 8 min SPECT data were obtained from the 40 min SPECT and 8 min/40 min whole brain ratio
In this study, in the microsphere model method, the SPECT data at 8 min were obtained from count ratios of 8 min/40 min whole brain planar images and 40 min SPECT data. But the radioactivities of 40 min SPECT scans are non-linear for CBF due to a significant clearance of IMP, and this could cause error. For this reason, a simulation of the CBF correlation between the two-compartment model analysis and the microsphere model method with count ratios of 8 min/40 min was also performed. Firstly, the brain radioactivity at 40 min, C_b(40 min) was generated for each CBF according to the two-compartment model equation (Eq. 2) with the standard input function as an arterial input function with the V_d value assumed to be 50 ml/ml. Secondly, for each count ratio of 8 min/40 min planar images, i.e., 0.6. 0.7, 0.8, or 0.9, CBF values were calculated by the microsphere model method (Eq. 5 and 6). The resultant microsphere model method CBF values were compared with those generated by two-compartment model analysis.

RESULTS

Figure 2 shows the simulation of the CBF correlation between the two-compartment model and the microsphere model. This indicated systematic underestimation of CBF values evaluated by the microsphere model anal-

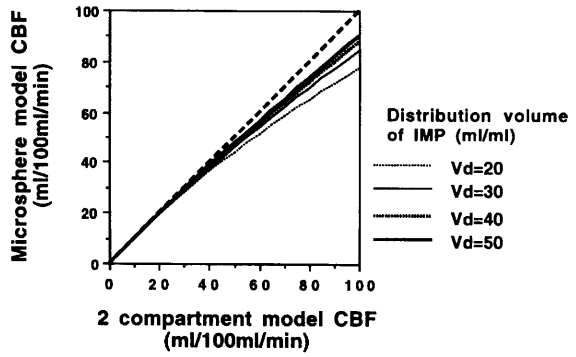

Fig. 2 Simulation of the CBF correlation between two-compartment model and microsphere model analyses, indicating systematic underestimation of CBF values evaluated by the microsphere model analysis as compared with those from the two-compartment model analysis (5.0% underestimation for CBF of 50 ml/100 ml/min and V_d of 50 ml/ml).

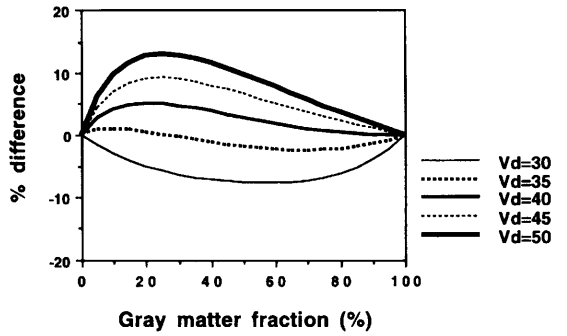

Fig. 3 Simulation of the effects of gray-white matter mixing on CBF values calculated by table look-up method. When the V_d value of gray and white matter was more than 40 ml/ml, CBF values calculated were systematically overestimated (9.8% for gray matter fraction of 50% and V_d of 50 ml/ml).

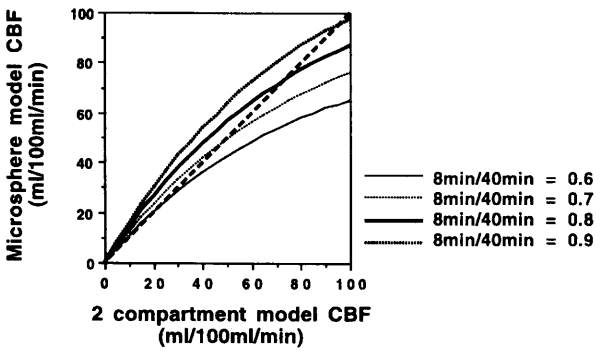

Fig. 4 Simulation of the CBF correlation between the two-compartment model analysis and microsphere model method using count ratios of 8 min/40 min planar images, i.e., 0.6, 0.7, 0.8, or 0.9. Overestimation of CBF values evaluated by the microsphere model method as compared with those from the two-compartment model analysis was observed in CBF ranges for the two-compartment model of 0.0–30.0, 0.0–45.0, 0.0–70.0 and 0.0–95.0 ml/100 ml/min with 8 min/40 min planar image count ratios of 0.6, 0.7, 0.8 and 0.9, respectively.

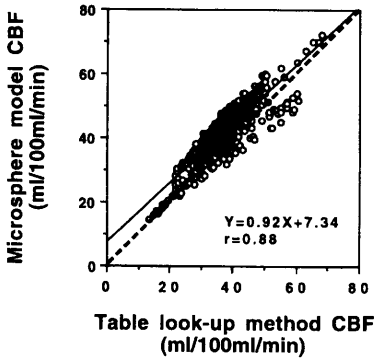

Fig. 5 Correlation between CBF values evaluated by the table look-up method and those from the microsphere model method. Underestimation of CBF values evaluated by the table look-up method as compared with those from the microsphere model method was observed (table look-up method: mean CBF ± S.D. = 37.4 ± 8.09 ml/100 ml/min, microsphere model method: mean CBF ± S.D. = 41.8 ± 8.46 ml/100 ml/min).

ysis as compared with those from the two-compartment model analysis. The magnitude of CBF underestimation was thus expected to be 5.0% for two-compartment model CBF of 50 ml/100 ml/min and V_d of 50 ml/ml.

Figure 3 shows the effects of gray-white matter mixing for CBF values calculated by the table look-up method. When the V_d value for gray and white matter was 30 ml/ml, calculated CBF values were systematically underestimated when the fraction of gray matter varied from 0 to 100%. But, when the V_d value for gray and white matter was more than 40 ml/ml, calculated CBF values were systematically overestimated (9.8% for gray matter fraction of 50% and V_d of 50 ml/ml).

Figure 4 shows the simulation of the CBF correlation between the two-compartment model and the microsphere model method in which 8 min SPECT data were obtained from the 40 min SPECT and 8 min/40 min whole brain count ratio. In this simulation, comparative overestimation of CBF values by the microsphere model method was observed in CBF ranges for the two-compartment model of 0.0–30.0, 0.0–45.0, 0.0–70.0 and 0.0–95.0 ml/100 ml/min with 8 min/40 min planar image count ratio of 0.6, 0.7, 0.8 and 0.9, respectively. In this study, the actual mean count ratio of the 8 min/40 min planar image was 0.762 ± 0.072 (± S.D.).

A good correlation was obtained between CBF values evaluated by the table look-up method and those from the microsphere model method (Y = 0.92X + 7.34, X: table look-up method, r = 0.88) (Fig. 5), but overestimation of CBF values was observed with the microsphere model method as compared with those from the table look-up method. Mean CBF values evaluated by the table look-up method were 10.6% lower than those from the microsphere model method (table look-up method: mean CBF ± S.D.

= 37.4 ± 8.09 ml/100 ml/min, microsphere model method: mean CBF ± S.D. = 41.8 ± 8.46 ml/100 ml/min).

V_d values were not uniform in the brain, especially low V_d values being observed in lesions, i.e., cerebral infarctions and contusions. The mean V_d value in X-ray CT normal density regions was 48.7 ± 9.15 ml/ml (± S.D.). There was no significant difference between gray and white matter in V_d values.

DISCUSSION

The microsphere model analysis has been routinely used as a method for measuring CBF using IMP, but underestimation of CBF is caused by significant clearance of IMP from the brain, especially when data acquisition is prolonged.[6–9] In this study, the simulation study similarly indicates systematic underestimation of CBF values with evaluation by microsphere model analysis as compared with those from the two-compartment model analysis even when data acquisition is limited to the early phase i.e., within 8 min after IMP infusion (5.0% underestimation for a two-compartment model CBF of 50 ml/100ml/min and V_d of 50 ml/ml) (Fig. 2).

The simulation of the effects of gray-white matter mixture also indicated differences between true CBF values (= 80 ml/100 ml/min × gray matter fraction + 20 ml/100 ml/min × white matter fraction) and table look-up method CBF values. In this study, the mean V_d value was 48.7 ± 9.15 ml/ml (± S.D.) for normal regions on X-ray CT. When the V_d value of gray and white matter was more than 40 ml/ml, the table look-up method CBF was systematically overestimated (9.8% for a gray matter fraction of 50% and a V_d of 50 ml/ml) (Fig. 3). On the other hand, there were no effects of gray-white matter mixing on CBF values calculated by the microsphere model analysis, because the correlation between the brain radioactivity and CBF value is linear in the microsphere model (Eq. 5).[17]

A good correlation was obtained between CBF values evaluated by the table look-up method and those from the conventional microsphere model method (Fig. 5), suggesting equivalent applicability, but while the two simulation studies (Figs. 2 and 3) indicated that CBF values obtained from the table look-up method would be higher than those from microsphere model analysis, in fact the opposite was the case. The microsphere model method values were thus actually 10.6% higher than the table look-up method CBF values (Fig. 5). As reasons for this, a number of factors must be considered.

One possibility is error in estimating the SPECT brain counts at 8 min in the microsphere model method with count ratios 8 min/40 min whole brain planar images and 40 min SPECT data.[18] This error would be caused by non-linearity of 40 min SPECT radioactivities due to a significant clearance of IMP. The simulation study (Fig. 4) revealed comparative overestimation of CBF values by the microsphere model method in CBF ranges for the two-compartment model of 0.0–30.0, 0.0–45.0, 0.0–70.0 and 0.0–95.0 ml/100 ml/min with 8 min/40 min planar image count ratios of 0.6, 0.7, 0.8 and 0.9, respectively. In this study, the actual mean count ratio of the 8 min/40 min planar image was 0.762 ± 0.072 (± S.D.), and therefore this could have been responsible for the overestimation of CBF values determined by the microsphere model method. In addition, other unknown errors due to radioactivities from extracerebral arteries included in 8 and 40 min planar images could have played roles.

Another potential source of error is in the determination of the arterial input function. For accurate CBF measurement, accurate determination of this function including corrections for time delay and dispersion of input is required. It has been shown in the $H_2{}^{15}O$ PET studies that no correction for these is associated with greater overestimation of CBF when the scan duration is shorter.[19–21] The standard input function used in table look-up method does not feature these corrections, because errors from time delay and dispersion would not be significant due to the sufficient delay until the mid-scan time of the two SPECT scans, i.e., 40 and 180 min,[10–12] but these errors in the microsphere model analysis case will be more significant, because the scan time was very early at 8 min. This could have directly caused the overestimation of CBF values determined by the microsphere model analysis. With the table look-up method, on the other hand, there might have been unknown errors due to difference in the arterial input curve shape for each subject.

In conclusion, a relatively good correlation was obtained between CBF values gained by table look-up method and those from the conventional microsphere model method. Since the table look-up method is simple, and does not require a continuous arterial blood sampling, it can be recommended for routine application. Possible reasons for the contrast to expectations from theoretical considerations, higher CBF values from the microsphere model method than the table look-up method are:

1. Errors in estimation of SPECT data at 8 min by calibration of SPECT scan at 40 min with count ratios of 8 min/40 min whole brain planar images in the microsphere model method.
2. Errors in determination of arterial input function with both methods.

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