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# Error analysis of autoradiography method for measurement of cerebral blood flow by $^{123}$I-IMP brain SPECT: A comparison study with table look-up method and microsphere model method

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N-isopropyl-p-[$^{123}$I]iodoamphetamine (IMP) has been commonly used as a cerebral blood flow tracer, but, significant clearance of IMP from the brain to the blood causes underestimation of cerebral blood flow (CBF) as compared with true CBF when the conventional microsphere model method is applied. Previously, we reported an "Autoradiography method" (ARG method) for measuring CBF by using IMP in which this clearance effect was corrected. This method was based on a two-compartment model (influx: $K_1$, efflux: $k_2$, $K_1/k_2$ = distribution volume of IMP ($V_d$)), the $K_1$ (corresponding to CBF) being obtained from the table which showed a correlation between CBF and the brain counts of SPECT scan with a constant $V_d$ value. 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, the ARG method was compared with the table look-up method (TLU method) and the conventional microsphere model method (MS method) for 30 subjects. When the $V_d$ value in the ARG method was assumed to be 50 m*l*/m*l*, CBF values obtained by the ARG method were correlated well with those obtained by the TLU method ($Y = 1.04X - 2.5$; $X$: TLU, $Y$: ARG, $r = 0.97$) and those obtained by the MS method ($Y = 0.82X + 12.1$; $X$: ARG, $Y$: MS, $r = 0.84$). But, when the $V_d$ value was assumed to be more or less than 50 m*l*/m*l*, ARG method CBF were under- or overestimated compared with the TLU method. This indicated that the ARG method could be a reliable method for CBF measurement if the $V_d$ was determined properly. CBF values obtained by the MS method were actually 13.2% higher than those obtained by the ARG method against previous studies. As reasons for this, errors in the effects of gray-white matter mixture in the ARG method and in estimation of the SPECT brain counts at 8 min in the MS method were considered.

**Key words:** IMP, SPECT, cerebral blood flow, autoradiography method

## INTRODUCTION

Iodine-123 labeled N-isopropyl-p-iodoamphetamine (IMP) has been 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 its significant clearance from the brain caused a change in IMP distribution[3,4] and underestimation of CBF when a conventional microsphere model method[5] was applied to prolonged data acquisition.[6–9] Previously, we reported an "Autoradiography method" (ARG method) with IMP, a new simple approach to the measurement of CBF, in which this clearance effect was corrected.[10,11] This approach was based on a two-compartment model (influx: $K_1$, efflux: $k_2$, $K_1/k_2$ = distribution volume of IMP ($V_d$)) in which the $V_d$ value was assumed to be constant, and the $K_1$ value (corresponding to CBF) was obtained from the table which showed a correlation between CBF and the brain counts of the SPECT scan (mid-scan time: 40 min).

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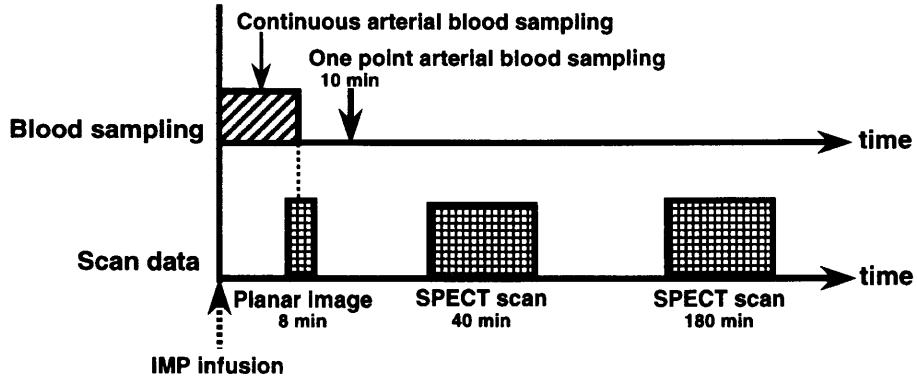



**Fig. 1** The experimental protocol design shows the time schedule of scan and blood sampling. The one point arterial blood sampling from the brachial artery is performed at 10 min after IMP infusion for determination of arterial input function for TLU and ARG method. Continuous arterial blood sampling from the brachial artery is also performed over the 8 min after IMP infusion for MS method. Two SPECT scans are performed at mid-scan time of 40 and 180 min after IMP infusion for TLU (40 min, 180 min), ARG (40 min) and MS (40 min) methods. Brain planar images over 50 sec are obtained at 8 min after IMP infusion for MS method.

Arterial input function was obtained by calibrating against the standard input function from one point arterial blood sampling at 10 min after intravenous infusion of IMP. It has been considered that the CBF value obtained by the ARG method would vary according to the assumed $V_d$ value, and the $V_d$ value would be dependent on the intrinsic performance of the SPECT scanner.[10] Previously, we also reported a "Table look-up method" (TLU method) with IMP.[12–14] This TLU method was also based on a two-compartment model, in which CBF and $V_d$ pair could be obtained from two SPECT scans and one point arterial blood sampling. The purpose of the present study was to compare the ARG method with the TLU method and with the conventional microsphere model method (MS method)[15] for a major patient series.

## MATERIALS AND METHODS

*Subjects*

SPECT studies were performed in 30 subjects including 19 patients with cerebral contusion, 3 with cerebrovascular disease, 2 with hypoxic brain, 2 with carbon monoxide toxicosis and 4 normal volunteers. None of the patients had any heart or lung disease. A informed consent was obtained from each subject.

*SPECT study*

Two SPECT scans were performed, at 40 min and 180 min of mid-scan time, after intravenous infusion of 222 MBq IMP for 1 min. Planar brain images for 50 sec were obtained at 8 min after IMP infusion for the conventional microsphere model method (MS method) (Fig. 1). The SPECT scanner used was a Neurocam (Yokogawa Medical Systems Corp., Tokyo, Japan),[16] 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 with low energy high resolution (LEHR) collimators. The SPECT scan protocol acquired 64 projections at 50 sec per projection with 120° rotation of the camera. Reconstruction was performed by filtered backprojection with a Butterworth filter (cutoff frequency 0.45 cycle/cm, power factor 10).[17] Attenuation correction was made numerically by assuming the object shape to be circular or elliptical and the attenuation coefficient to be uniform (0.12 $cm^{-1}$) (Sorenson's method[18]). The scattered photons were not corrected. 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 autoradiography method (ARG method) and the table look-up method (TLU method). 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 MS method (Fig. 1).

A cross calibration scan was performed with 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 were placed in the cerebellum, pons, thalamus, putamen, centrum semiovale and cerebral cortex including frontal, temporal, parietal and occipital lobes on the 40 and 180 min SPECT images. The shape of regions-of-interest was circular: 35 mm diameter for the cerebellum, and elliptic with short axes of 16–25 mm and

long axes of 25–50 mm for other regions.

*Theory*

*Autoradiography method (ARG method)*[10,11]: In this method, a two-compartment model was employed in line with previous reports.[6–8,19,20]

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

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[1,2,21] and therefore, $K_1$ equals CBF. The ratio of $K_1$ to $k_2$ is called the distribution volume of IMP ($V_d$ (ml/ml)).

Solving Eq. 1 provides:

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

where $\otimes$ denotes the convolution integral.

For a given $V_d$ value ($= K_1/k_2$) and a given arterial input function, $C_a(t)$, Eq. 2 provides a unique relation between $C_b(t)$ and $K_1$; then $K_1$ values (corresponding to CBF) are obtained. 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.

*Table look-up method (TLU method)*[12–14]: In this method, a two-compartment model was also employed. For this method, two SPECT scans were performed. The model equation (Eq. 2) can therefore be expressed for each scan.

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

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

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

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

For a given arterial 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 $k_2$. Then, for a given radioactivity ratio of first to second scans, the table look-up procedure provides a corresponding $k_2$ value, and the $K_1$ value can be calculated by inserting this $k_2$value into Eq. 3a. The arterial input function is obtained by one point arterial blood sampling as in the ARG method.

*Microsphere model method (MS method)*[15]: 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

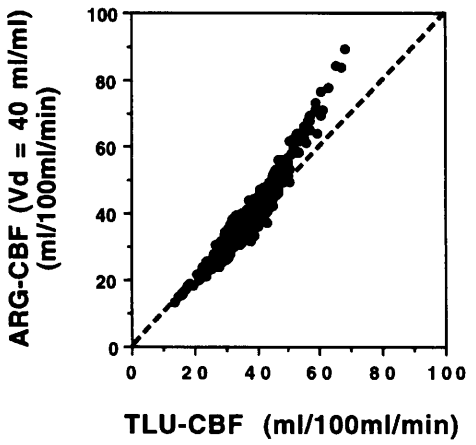
In this study, SPECT data at 8 min ($C_b$) were 40 min SPECT data calibrated by the count ratio of 8 min/40 min whole brain planar images.

*Simulation of the effects of gray-white matter mixture*

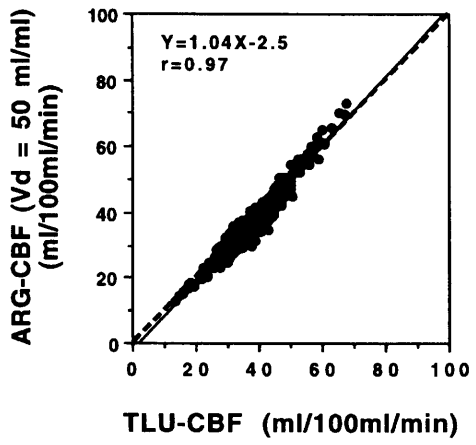
The limited spatial resolution of the SPECT scanner causes a gray-white matter mixture in regions-of-interest. The effects of gray-white matter mixing on CBF values calculated by the ARG method were evaluated.[22] Brain counts in heterogeneous tissue on a 40 min SPECT scan were generated as mixtures of gray and white matter. CBF values for the gray and white matter were assumed to be 80 and 20 ml/100 ml/min, respectively. The $V_d$ value for gray and white matter was assumed to be the same as 40, 50 or 60 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 the ARG method by using 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 ARG method.

## RESULTS

Figure 2a–2c show correlations between CBF values by TLU method and those by the ARG method in which the $V_d$ values were assumed to be 40, 50 and 60, respectively. When the $V_d$ value in the ARG method was assumed to be 50 ml/ml, the best correlation and good linearity between the TLU and ARG methods were observed ($Y = 1.04X - 2.5$; $X$: TLU, $Y$: ARG, r = 0.97) (Fig. 2b) and these values for the two methods were consistent. However, when the $V_d$ value was assumed to be 40 or 60 ml/ml, the ARG method CBF was over- (Fig. 2a) and under- (Fig. 2c) estimated compared with the TLU method CBF, respectively, in particular in the hyperperfusion region. The mean CBF values obtained by the ARG method for all regions-of-interest data were 39.1 ± 10.3, 36.3 ± 8.6 and




a

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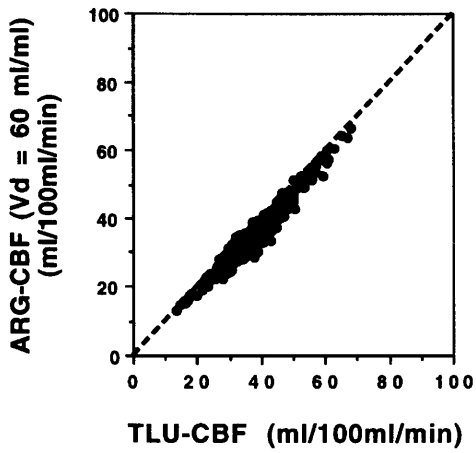


c

**Fig. 2** Figures show correlations between CBF values by TLU method and those by ARG method in which the $V_d$ value is assumed to be 40 (a), 50 (b) or 60 (c). When the $V_d$ value in ARG method is assumed to be 50 m*l*/m*l*, the best correlation is observed ($Y = 1.04X - 2.5$; $X$: TLU, $Y$: ARG, r = 0.97) (b). The dot line is identity.

34.8 ± 7.8 m*l*/100 m*l*/min (± S.D.) when the $V_d$ values were assumed to be 40, 50 and 60 m*l*/m*l*, respectively. The mean CBF value by the TLU method was 37.4 ± 8.1 m*l*/

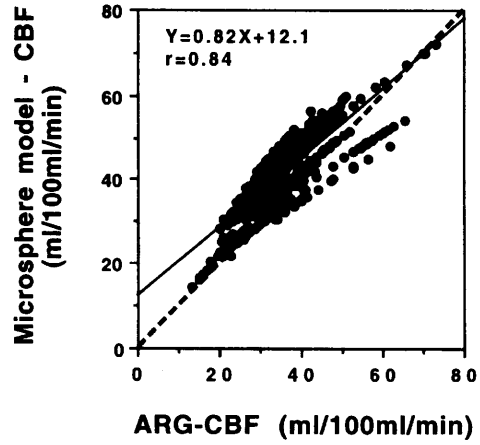


**Fig. 3** Correlation between CBF values evaluated by ARG method in which the $V_d$ value is assumed to be 50 m*l*/m*l* and those from MS method. A good correlation is obtained ($Y = 0.82X + 12.1$; $X$: ARG, $Y$: MS, r = 0.84). However, overestimation of CBF values is observed with MS method as compared with those from ARG method. The dot line is identity.

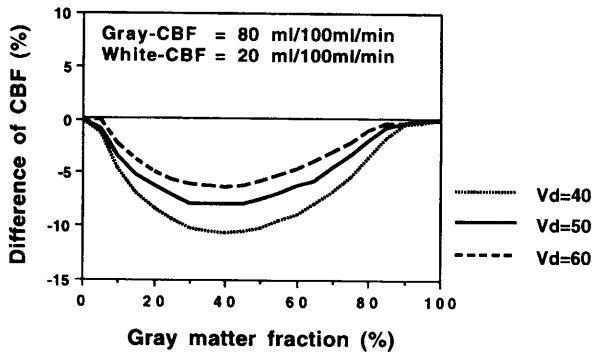


**Fig. 4** Simulation of the effects of gray-white matter mixing on CBF values calculated by ARG method. For each $V_d$ value, CBF values calculated are systematically underestimated (−7.6% for a gray matter fraction of 50% and a $V_d$ of 50 m*l*/m*l*).

100 m*l*/min (± S.D.).

The mean $V_d$ value evaluated by the TLU method in X-ray CT normal density regions was 48.7 ± 9.15 m*l*/m*l* (± S.D.). There was no significant difference between gray and white matter in $V_d$ values.

A good correlation was obtained between CBF values evaluated by the ARG method in which the $V_d$ value was assumed to be 50 m*l*/m*l* and those by the MS method ($Y = 0.82X + 12.1$; $X$: ARG, $Y$: MS, r = 0.84) (Fig. 3). However, overestimation of CBF values was observed with the MS method as compared with the ARG method. Mean CBF values evaluated by the ARG method were 13.2% lower than those by the MS method (mean MS method CBF: 41.8 ± 8.5 m*l*/100 m*l*/min (± S.D.)).

Figure 4 shows the effects of gray-white matter mixing for CBF values calculated by the ARG method. For each Vd value, CBF values calculated were systematically

underestimated when the fraction of gray matter was varied from 0 to 100% (−7.6% for a gray matter fraction of 50% and a $V_d$ of 50 ml/ml).

## DISCUSSION

The best correlation between the TLU and ARG methods was observed (Fig. 2b) when the $V_d$ value in the ARG method was assumed to be 50 ml/ml which was almost the same as the mean $V_d$ value evaluated by the TLU method. These ARG method values also closely agreed with the MS method values (Fig. 3). However, this $V_d$ value was larger than those in previous studies, i.e., 22 in man,[5] 22 in rat[23] and 29.6 in man[8] (ml/ml). As reasons for this discrepancy, the differences in the reconstruction algorithm, the attenuation correction method and the scattered photons correction method for each SPECT scanner system were considered.[10] These indicated that the $V_d$ value in the ARG method should be determined for each SPECT scanner system by using an other method, e.g., the TLU method, since the reconstruction algorithm, the attenuation correction method and the scattered photons correction method were different for each SPECT scanner system.

$V_d$ values in the normal brain tissue might be almost constant, but it was reported that $V_d$ values in the pathological regions, e.g., cerebral infarction were lower than those in normal regions.[14,19,20] In the present study, all regions-of-interest in the pathological regions, e.g., cerebral contusion and cerebral infarction showed low $V_d$ values and hypoperfusion. Since in hypoperfusion regions accurate CBF values could be calculated by the ARG method in any assumed $V_d$ values,[10] a good correlation was observed between the ARG and TLU methods (Fig. 2b). However, if there were hyperperfusion lesions with low or high $V_d$ values, the error in measuring CBF by the ARG method would be significant.

While the MS method was routinely used as a method for measuring CBF by means of IMP, the underestimation of CBF was caused due to significant clearance of IMP from the brain.[6–9,24] In this study, a good correlation was obtained between CBF values evaluated by the ARG method and those by the MS method (Fig. 3), suggesting equivalent applicability. However, CBF values obtained with the MS method were actually 13.2% higher than those obtained with the ARG method against previous studies.[6–9,24]

One possibility is error in the effects of gray-white matter mixture. Simulation of the effects of gray-white matter mixture indicated differences between true CBF values and CBF values calculated by the ARG method. In this simulation, CBF values calculated were systematically underestimated (−7.6% for a gray matter fraction of 50% and a $V_d$ of 50 ml/ml) (Fig. 4). On the other hand, there were no effects of gray-white matter mixing on CBF values calculated by the MS method, because the correlation between the brain radioactivity and CBF value is linear in the microsphere model (Eq. 5).[22]

Another potential source of error is in estimation of the SPECT brain counts at 8 min in the MS method with count ratios of 8 min/40 min whole brain planar images and 40 min SPECT data.[24–26] This error would be caused by nonlinearity of 40 min SPECT counts due to a significant clearance of IMP which had been described in our report.[24] An additional potential source of error is the determination of the arterial input function, i.e., corrections for time delay and dispersion of input for two methods[27–29] and unknown errors due to differences in the arterial input curve shape for each subject for the ARG method.[24]

In conclusion, the best correlation between the TLU and ARG methods was observed when the $V_d$ value in the ARG method was assumed to be 50 ml/ml which was almost the same as the mean $V_d$ value evaluated by the TLU method. These ARG method values closely agreed with conventional MS method values, suggesting equivalent applicability. This indicates that the $V_d$ value in the ARG method should be determined properly for each SPECT scanner system by using an other method, e.g., the TLU method. CBF values obtained by the MS method were actually 13.2% higher than those obtained by the ARG method against previous studies. As reasons for this, errors in the effects of gray-white matter mixture in the ARG method and in estimation of the SPECT brain counts at 8 min in the MS method were considered.

## ACKNOWLEDGMENTS

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