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Measurement of regional cerebral blood flow with ^{123}I-IMP using one-point venous blood sampling and causality analysis: Evaluation by comparison with conventional continuous arterial blood sampling

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Objective: Arterial input function represents the delivery of intravascular tracer to the brain. The optimal setting of this function is essential for measuring regional cerebral blood flow (rCBF) based on the microsphere model using *N*-isopropyl-4-[^{123}I]iodoamphetamine (^{123}I-IMP), in which the arterial ^{123}I-IMP concentration (integral value) during the initial 5 min is usually applied. We developed a novel method in which the arterial ^{123}I-IMP concentration is estimated from that in venous blood samples. ***Methods:*** Brain perfusion SPECT with ^{123}I-IMP was performed in 110 patients with disorders of the central nervous system. A causality analysis determined the relationship between various SPECT parameters and the ratio of the octanol-extracted arterial radioactivity concentration during the first 5 min (Caoct) to the octanol-extracted venous radioactivity concentration at 27 min after an intravenous injection of ^{123}I-IMP (Cvoct). The Caoct/Cvoct value was estimated using various SPECT parameters and compared with the directly measured value. ***Results:*** The measured and estimated values of Caoct/ Cvoct ($r = 0.856$, $n = 50$) closely correlated when the following 7 parameters were included in the regression formula: radioactivity concentration in venous blood sampled at 27 min (Cv), Cvoct, Cvoct/Cv, and 4 parameters related to cerebral tissue accumulation that were measured using a four-head gamma camera 5 and 28 min after ^{123}I-IMP injection. Furthermore, the rCBF values obtained using the input function estimated by this method also closely correlated with the rCBF values measured using the continuous arterial blood sampling ($r = 0.912$, $n = 180$). ***Conclusion:*** These results suggest that this method would serve as a convenient and less invasive method of rCBF measurement in the clinical setting.

Key words: regional cerebral blood flow, ^{123}I-IMP, SPECT, venous sampling, causality analysis

INTRODUCTION

CEREBRAL PERFUSION SCINTIGRAPHY using *N*-isopropyl-4-[^{123}I]iodoamphetamine (^{123}I-IMP) has been widely used in the diagnosis, estimation of prognosis, and assessment of therapeutic effects against various diseases of the central nervous system. Single photon emission computed tomography (SPECT) can determine the three-dimensional distribution of cerebral blood flow. Quantitative cerebral perfusion SPECT is applied to obtain regional cerebral blood flow (rCBF) when patients are followed up to search for rCBF changes or when an intervention is performed (e.g., neuroactivation or pharmacological intervention). Although several quantitative techniques including continuous[1–8] and one-point (table look-up and autoradiography methods)[9–15] arterial blood sampling methods have been introduced, they are not

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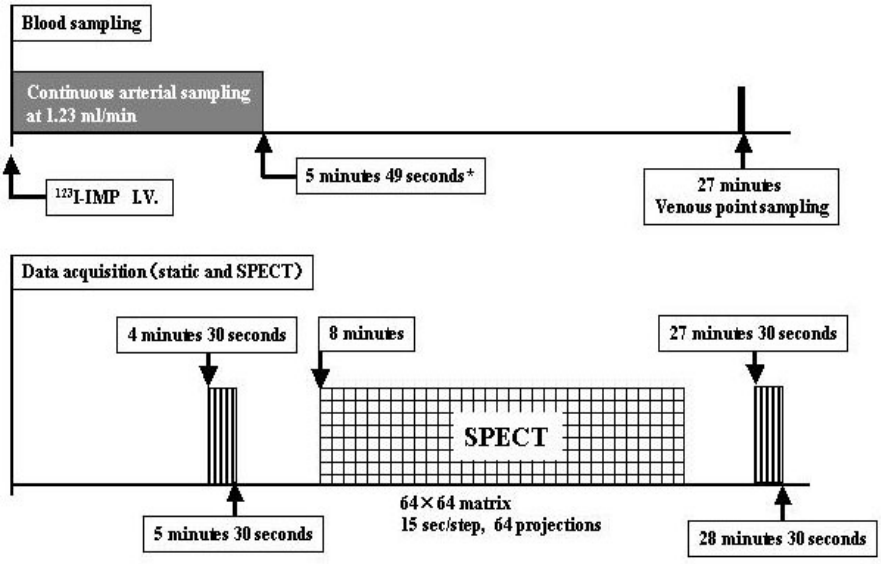

Fig. 1 Time schedule of SPECT, static imaging, arterial and venous blood sampling after ^{123}I-IMP injection. Checkered box represents SPECT imaging and striped boxes represent static imaging for one minute centered at 5 and 28 minutes. *Time correcting for sampling tube volume between the artery and pump is 49 sec.

widely applied in the clinical setting because they are invasive and complex. Several less invasive means of quantifying an input function using values from venous samples have been attempted,[16–20] but none is generally accepted as a routine method of rCBF measurement.

We recently validated a method of deriving a multifactor regression equation on time-series and causality between input (arterial sample) and output (venous sample) values of ^{123}I-IMP using neural network techniques.[21] In the present study, we modified the previous method of calculating rCBF from venous sample values by determining a function that represents the relationships among arterial and venous sample values, and indicators of changes in radioactivity in cerebral tissue over time using multiple regression analysis. The possibility of applying this method in the clinical setting was examined by comparing the rCBF value calculated with the input function estimated from this method with that obtained by a modification of the conventional microsphere model described by Kuhl et al.[2,7,8]

PATIENTS AND METHODS

Patients

We recruited 110 patients (54 male and 56 female; mean age, 65.7 ± 15.6 y; mean ± standard deviation [SD]; range, 17–89 y) with the following conditions of the central nervous system: Alzheimer's type dementia (n = 23), cerebral infarction (n = 31), Parkinson's disease (n = 26) and other diseases (n = 30). Informed consent was obtained from all participants after the nature of the procedures had been fully explained.

Data collection and image processing

Data were collected using a four-head gamma camera (Gamma View SPECT 2000H-40; Hitachi Medico, Tokyo, Japan) equipped with a low energy general purpose (LEGP) collimator compatible with ^{123}I photon energy.

Static images were simultaneously collected in frame mode from 4 directions with a matrix size of 64 × 64 (3.4 mm/pixel) and at a rate of 30 seconds per frame. The average whole brain radioactivity at 5 (Cb_5, counts/min/pixel) and 28 (Cb_{28}, counts/min/pixel) minutes was determined by summation of the image data for 1 minute centered at these time points. The whole brain region was accurately delineated using static images obtained during 5 minutes and 30 seconds after ^{123}I-IMP injection. The mean value of the counts collected from all of 4 directions, or from the front, back, and both sides, was used as whole brain radioactivity. The amount of radioactivity at 17 minutes, which is the median time of SPECT collection (Cb_{17}, counts/min/pixel), was calculated as the mean value of Cb_5 and Cb_{28}, and the increase in the whole brain radioactivity for 23 minutes between 5 and 28 minutes ($Cb_{28\text{-}5}$, counts) is the difference between Cb_{28} and Cb_5.

At 8 minutes after ^{123}I-IMP administration, we started to collect SPECT images for a period of 16 minutes, using a 64 × 64 matrix from 64 directions at a rate of 15 seconds per direction. The data from the 4 detectors were combined to reconstruct images using a Ramachandran filter as a convolution correction function and a Winner filter (m: 2.5 and Pn/Ps: 0.15) as a preprocessing filter, with no correction for absorption and scattering. Figure 1 shows the schedule for image and blood collection.

Blood collection and measurement of radioactivity

A 24-gauge plastic needle was inserted into the left brachial artery to collect arterial blood using a continuous blood-sampling device (Harvard infusion/withdrawal pump, Model 944; South Natick, Massachusetts) at a constant rate (1.23 m*l*/min) for 5 minutes and 49 seconds immediately after the intravenous injection of ^{123}I-IMP. The 49 sec represents the period correcting for sampling tube volume between the artery and the pump. ^{123}I-IMP was quickly administered at a dose of 167 or 222 MBq into the right median cubital or central vein, and immediately flushed with about 10 m*l* of physiological saline. A dose of 167 MBq was given to patients who weighed 50 kg or less and 222 MBq for those 51 kg and above. About 5 m*l* of venous blood was collected from the cutaneous vein of the right forearm, so that the median time would be 27 minutes after the administration of ^{123}I-IMP. The venous blood sampling point was positioned at least 3 cm peripherally to the ^{123}I-IMP administration site.

Arterial and venous blood samples were dispensed in triplicate as 0.5 m*l* aliquots into centrifuge tubes containing 5.0 m*l* of octanol, vortex-mixed and then separated by centrifugation for 5 minutes at 2,500 rpm. A portion (1 m*l*) of each supernatant was transferred to another tube and then the amount of radioactivity in three samples each of arterial and venous whole blood and their supernatants (12 samples in total), as well as in three background test tubes was measured for 10 minutes using a well counter (Auto-Well Gamma System ARC-360, Aloka, Tokyo, Japan). After subtracting the background count and correcting for radioactive decay and sampling tube volume, the mean counts in the arterial and venous whole blood samples and their supernatants were calculated to determine the concentration of radioactivity in arterial blood (Ca, counts/min/m*l*), in octanol-extracted arterial blood (Caoct, count/min/m*l*), in venous blood (Cv, counts/min/m*l*), and in octanol-extracted venous blood (Cvoct, counts/min/m*l*). We also determined the octanol extraction rates of arterial and venous blood samples (Na and Nv).[2]

Examination of validity of multiple regression analysis

Causality between input and output signals to brain over time was observed using 6 parameters related to the blood (Ca, Caoct, Cv, Cvoct, Na, and Nv) and 4 related to cerebral tissue accumulation (Cb_5, Cb_{28}, Cb_5/Cb_{17}, and $Cb_{28\text{-}5}$). All parameters were derived from the readily available variables that are generally used in rCBF quantitation using ^{123}I-IMP and continuous arterial blood sampling.

The ratio of Caoct, an important input signal, to Cvoct, an important output signal, was considered an objective variable, and the relationship between the Caoct/Cvoct ratio and the 10 parameters was examined by multiple regression analysis as described below: $Caoct/Cvoct = A \cdot Ca + B \cdot Caoct + C \cdot Cv + D \cdot Cvoct + E \cdot Na + F \cdot Nv + G \cdot Cb_5 + H \cdot Cb_{28} + I \cdot (Cb_5/Cb_{17}) + J \cdot Cb_{28-5} + K$, where A to K are the coefficients of the regression formula. We then examined the relationship between the Caoct/Cvoct value calculated directly from measured values and that estimated from multiple regression analysis.

The relationship between the directly calculated and estimated values of Caoct/Cvoct was also examined when continuous arterial blood sampling-related parameters were omitted and the remaining 7 parameters (Cv, Cvoct, Nv, Cb_5, Cb_{28}, Cb_5/Cb_{17}, and $Cb_{28\text{-}5}$) were applied.

Values were calculated from data derived from 50 patients randomly-selected from among all 110.

Comparative examination of regional cerebral blood flow

To evaluate the feasibility of applying this method in a clinical setting, the relationship between rCBF calculated using continuously sampled arterial and venous blood values was examined using data from the remaining 60 patients. Three regions of interest (ROI) were examined for each patient. We calculated rCBF from continuously-sampled arterial blood values using the formula,[1]

$$Fa = 100 \cdot R \cdot Cb/(Na \cdot Ca \cdot T \cdot R) = 100 \cdot Cb/Caoct \cdot T \quad (1)$$

where Fa represents rCBF value (m*l*/100 g/min), R is the continuous blood sampling rate (1.23 m*l*/min), Cb is the amount of radioactivity (counts/min/g) in cerebral tissue, T is the blood collection time (min), Ca is the concentration of radioactivity in whole arterial blood and Na is the octanol extraction rate of the arterial blood sample. The assumed specific gravity of brain tissue was 1.0. The Cb value was determined by multiplying the cross-calibrated SPECT value by the radioactivity ratio in the whole brain (Cb_5/Cb_{17}). The gamma counter was cross calibrated with the SPECT by measuring standard ^{123}I-IMP solutions of different concentrations in each system and converting the SPECT values to counter values using a linear equation calculated by the least squares fit method.

To calculate the value of rCBF based on that of the venous blood sample (Fv, m*l*/100 g/min), Caoct in the equation (1) was substituted by the estimated value. The Caoct value was estimated using the 7 parameters remaining after omitting those that were related to continuous arterial blood sampling from the 10 parameters. That is, Caoct was estimated by multiplying the estimated Caoct/Cvoct value, which was derived from the regression formula obtained in the present study, by the directly measured Cvoct value. The rCBF value was also calculated using the method described by Fujioka et al.[20] and the Cvoct value obtained in the present study (Fv′, m*l*/100 g/min).

We then compared the rCBF values among these three methods and the correlations of Fv and Fv′ with Fa.

Variable used in the present study are summarized in Table 1.

Table 1 Variables used in the present study

Variables	Explanation	Unit
Ca	Arterial radioactivity concentration	counts/min/m*l*
Caoct	Octanol-extracted arterial radioactivity concentration	counts/min/m*l*
Cv	Venous radioactivity concentration	counts/min/m*l*
Cvoct	Octanol-extracted venous radioactivity concentration	counts/min/m*l*
Na	Arterial octanol extraction ratio	
Nv	Venous octanol extraction ratio	
Cb_5	Average whole brain radioactivity at 5 min	counts/min/pixel
Cb_{28}	Average whole brain radioactivity at 28 min	counts/min/pixel
$Cb_{28\text{-}5}$	Increase of average whole brain radioactivity from 5 to 28 min	counts/min/pixel
Cb	SPECT brain radioactivity	counts/min/g
Fa	rCBF estimated by continuous arterial sampling method	m*l*/100 g/min
Fv	rCBF estimated by venous sampling method in the present study	m*l*/100 g/min
Fv′	rCBF estimated by venous sampling method previously reported by Fujioka et al.	m*l*/100 g/min

Table 2 Mean, SD and CV of variables used for multiple regression analysis*

Variables	Mean	SD	CV (%)
Ca	2.96×10^5	7.46×10^4	25.2
Caoct	2.45×10^5	6.63×10^4	27.1
Cv	3.55×10^4	9.20×10^3	25.9
Cvoct	2.27×10^4	7.35×10^3	32.3
Na	8.24×10^{-1}	3.55×10^{-2}	4.30
Nv	6.31×10^{-1}	7.76×10^{-2}	12.3
Cb_5	9.43×10	2.55×10	27.1
Cb_{28}	1.35×10^2	3.36×10	25.0
Cb_5/Cb_{17}	8.22×10^{-1}	5.26×10^{-2}	6.40
$Cb_{28\text{-}5}$	4.04×10	1.50×10	37.2
Caoct/Cvoct	1.19×10	4.74	39.9

*SD, standard deviation; CV, coefficient of variation; n = 50.

Table 3 Coefficients of multiple regression formulae

Coefficients	Number of explanatory variables	
	10	7
A, coefficient of Ca	7.17×10^{-5}	
B, coefficient of Caoct	-4.38×10^{-5}	
C, coefficient of Cv	-1.44×10^{-3}	-1.46×10^{-3}
D, coefficient of Cvoct	1.70×10^{-3}	1.71×10^{-3}
E, coefficient of Na	2.78×10	
F, coefficient of Nv	-7.46×10	-7.02×10
G, coefficient of Cb_5	5.14×10^{-1}	−1.73
H, coefficient of Cb_{28}	-4.95×10^{-1}	1.85
I, coefficient of Cb_5/Cb_{17}	-1.64×10	-4.43×10
J, coefficient of $Cb_{28\text{-}5}$	4.48×10^{-1}	−1.98
K, constant	5.13×10	9.89×10

Statistical analysis

The difference between estimated and directly measured Caoct/Cvoct values was assessed using a paired-t test. The difference in rCBF values among methods was compared using a paired-t test considering Fa as the gold standard. The relationships between methods were assessed using Pearson's correlation analysis, and correlation coefficients were compared using Fisher's z-transformation. Statistical significance was defined as $p < 0.05$. All data were statistically analyzed using the SPSS software, version 11.5 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Validity of multiple regression analysis

Table 2 shows the mean, SD, and coefficient of variation (CV) of the 10 parameters and Caoct/Cvoct. The CV value was smallest for Na at 4.30%, followed by Cb_5/Cb_{17} at 6.40%, Nv at 12.3%, Cb_{28}, Ca, Cv, Cb_5, Caoct, Cvoct, and $Cb_{28\text{-}5}$. The CV value was largest for Caoct/Cvoct at 39.9%.

Multiple regression analysis between the objective variable Caoct/Cvoct, and 10 parameters produced the relational expression (multiple regression formula) with the coefficients shown in Table 3. Figure 2 shows a high correlation between Caoct/Cvoct estimated using all 10 parameters and Caoct/Cvoct calculated from the measured values ($r = 0.978$, $p < 0.0001$; $y = 0.957x + 0.513$). The mean and SD of the estimated and directly measured Caoct/Cvoct were close at 11.9 ± 4.74 and 11.9 ± 4.64, respectively ($p = 0.997$).

We then reduced the parameters of the explanatory variables and evaluated the validity of the multiple regression analysis. Coefficients of the multiple regression formula are shown in Table 3. Figure 3 shows a close correlation between Caoct/Cvoct estimated with the 7 parameters and the directly measured Caoct/Cvoct ($r = 0.856$, $p < 0.0001$; $y = 0.733x + 3.181$). The mean and SD of the estimated Caoct/Cvoct was 11.9 ± 4.06, which was not significantly different from that of directly measured Caoct/Cvoct ($p = 0.999$).

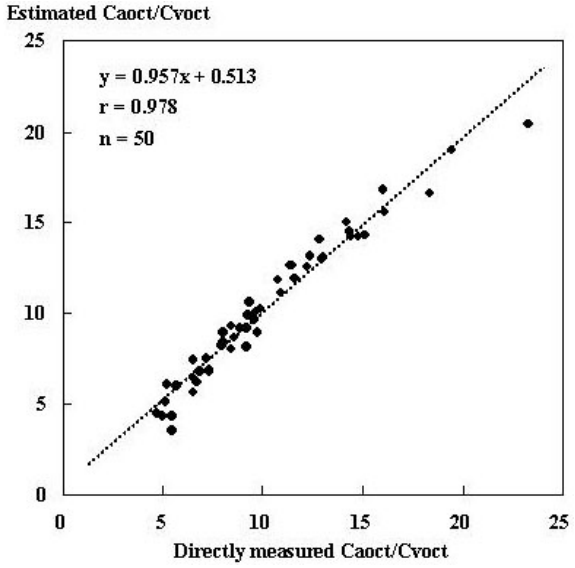

Fig. 2 Relationship between directly measured Caoct/Cvoct ratio and that estimated using 10-parameter regression analysis.

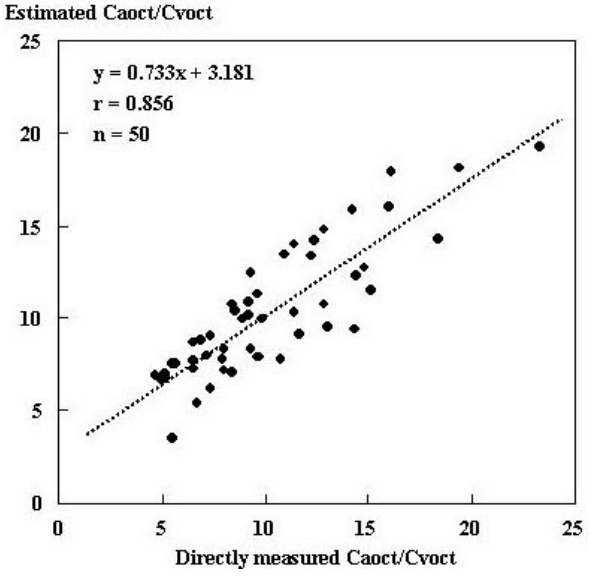

Fig. 3 Relationship between directly measured Caoct/Cvoct ratio and that estimated using 7-parameter regression analysis.

Comparative examination of regional cerebral blood flow
Figure 4 shows a close correlation between Fv and Fa when 7 parameters (Cv, Cvoct, Nv, Cb_5, Cb_{28}, Cb_5/Cb_{17}, and $Cb_{28\text{-}5}$) were used as the explanatory variables in the regression formula ($r = 0.912$, $p < 0.0001$; $y = 0.889x + 3.20$, $n = 180$). The mean ± SD values of Fa and Fv were almost identical at 26.77 ± 10.79 and 26.89 ± 10.51 ml/100 g/min, respectively ($p = 0.519$). On the other hand, the Fv′ value of 32.49 ± 14.62 significantly differed from Fa ($p < 0.0001$). The correlation between Fv′ and Fa was modest ($r = 0.789$, $p < 0.0001$, $n = 180$) and significantly lower than that between Fv and Fa ($p < 0.0001$).

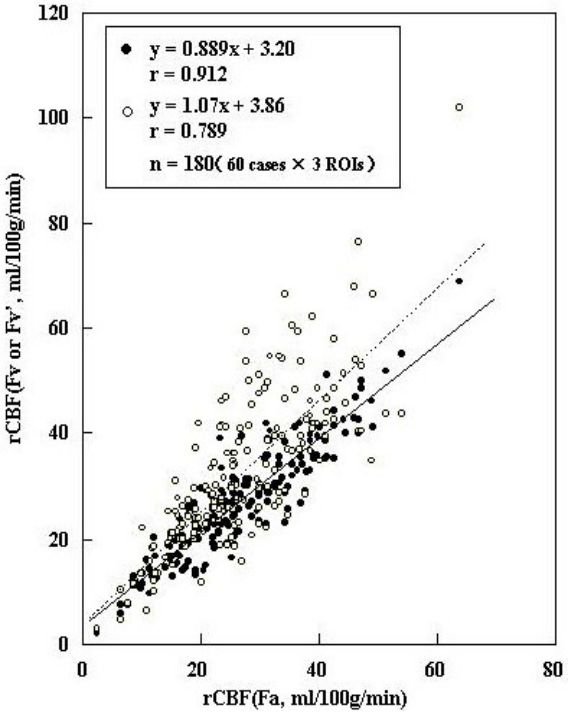

Fig. 4 Relationship between rCBF values estimated using one point venous blood sampling and those measured by conventional continuous arterial blood sampling (Fa). Values were estimated using methods presented here (Fv, *closed circles, solid line*) or described by Fujioka et al. (Fv′, *open circles, dashed line*).

DISCUSSION

We modified the previous method of estimating continuous arterial blood values of ^{123}I-IMP from venous blood values by determining a function that represents a correlation among many pieces of information obtained from individual patients using a multiple regression analysis.[21] Examination of the variance of all variables in 110 patients showed that Caoct/Cvoct had the highest CV. We therefore considered that it clearly represented individual differences and attempted to determine a function that represented causality between Caoct/Cvoct and the 10 parameters. The correlation between the Caoct/Cvoct values estimated with the obtained functional equation and from measured values was close. The result supports the notion that a function can be determined that represents causality between input and output signals over time.

To calculate an rCBF value without continuous arterial blood sampling, arterial blood-related parameters must be omitted. Therefore, we similarly attempted to determine this function using the 7 parameters remaining after omitting the arterial blood-related parameters. Since the correlation between the estimated and directly measured value of Caoct/Cvoct was close ($r = 0.856$), we considered

that the input function could be estimated by the 7 parameters. The results revealed a close correlation between Fv and Fa (r = 0.912), suggesting that the present method can be applied in clinical practice.

The parameters that we used to observe causality between input and output signals to the brain were derived from the readily available variables that are generally used in rCBF quantitation using ^{123}I-IMP and continuous arterial blood sampling. Use of all of available parameters for estimating Fv gave the best correlation with Fa, although the correlation remained significant after reducing the number of parameters (data not shown). Further studies might determine a factor(s) that will improve the accuracy of estimating the input function and rCBF.

Here, we randomly selected patients for cerebral perfusion SPECT who visited our department. The accuracy of the rCBF measurement did not apparently differ with respect to disease or age (data not shown). However, the tracer kinetics of ^{123}I-IMP in brain might be influenced by cardiopulmonary diseases or in young children, for whom the assumption of causality model presented here may not be established. Thus, the present method should be applied with care.

Fujioka et al.[20] have described a method in which the input function to the brain was estimated from the venous blood sampling value at 26 min. We used this method and calculated rCBF (Fv′) by substituting Cv instead of the venous blood sampling value at 27 min. Although the correlation was significant between Fv′ and Fa, it was lower than that reported by Fujioka et al. and also lower than that obtained using the method (Fv) presented here. This apparent discrepancy might be due to differences in the sampling site of the venous blood. Other investigators have reported that the venous concentration of a drug might change when venous blood is collected from the periphery of the upper limb or the opposite forearm or under heated conditions,[18,19] and a peripheral sampling site was adopted in the method of Fujioka et al. Here, we collected blood from a cutaneous vein in the forearm, which is a more proximal site than that in the method of Fujioka et al., because venous sampling at a peripheral site during a limited time period sometimes fails. Further study is necessary to clarify the effect of this factor on the accuracy of rCBF quantitation.

Regarding the timing for venous blood sampling, Ito et al.[19] examined timing by comparing data collected at 10, 20, 30, and 50 minutes after administration and found that venous blood sampling 20 minutes after the administration minimized the error of rCBF, and that the ratio of the venous to arterial radioactivity concentration reached equilibrium and became stable from around 30 minutes after administration. In the present study, venous blood sampling was completed within the specified period in only about half of the patients as time lags of about ±30 seconds or collection time prolonged by about 1 minute occurred with some patients. We therefore considered that ensuring venous access in advance is necessary to increase the accuracy of the venous blood sampling time.

Finally, since a four-head-type gamma camera was used in the present study, the radioactivity count of the whole brain was determined as the mean value of counts collected from the front, back, and both sides. When estimating Caoct/Cvoct using different types of gamma camera such as a single- or dual-head types, it will be necessary to determine their influence on the accuracy of estimation.

CONCLUSIONS

We modified the previous method of calculating rCBF with ^{123}I-IMP from venous blood sample values and determined a function that represents the relationship among arterial and venous blood sample values, and indicators of changes of radioactivity in cerebral tissue over time. The rCBF determined with the input function estimated using this method closely correlates with that determined with the input function obtained by continuous arterial blood sampling, suggesting that this method would serve as a convenient and less invasive method of rCBF measurement in the clinical setting.

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