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A new method to estimate rCBF using IMP and SPECT without any blood sampling

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We developed and evaluated a method to measure rCBF without any blood sampling by using iodine-123 IMP and SPECT. An integral of arterial input function, $\int_0^T Ca(t)dt$, can be expressed as TC(T)/CO, where TC(T) is radioactivity delivered to the body in T minutes and CO is cardiac output. If T is acceptably small, rCBF can be determined by means of a microsphere model analysis with IMP as Cb(T)/(TC(T)/CO), where Cb(T) is cerebral radioactivity at T minutes. We derived TC(T) and CO from a chest dynamic scan. The method was applied to 45 patients who underwent rCBF studies (58 studies) with arterial blood sampling (ABS). Data from the chest scan were analyzed in comparison with ABS data in the first 28 studies, and equations for correction yielding an accurate TC(T)/CO were derived. The validity of the proposed method was evaluated in the subsequent 30 studies. The method yielded rCBF (rCBF-test) which agreed well with rCBF obtained by a two-compartment model analysis of dynamic SPECT and ABS data (rCBF-ref) with the mean and SD of differences between rCBF-test and rCBF-ref being 1.0 and 2.7 ml/100 g/min, respectively. In eleven subjects who underwent more than two studies, a percentage change in rCBF-test between the studies also closely approximated that of rCBF-ref ($y = 1.11x + 2.63$, $r = 0.92$). The method can be used with acceptable reliability to measure rCBF without any blood sampling.

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

INTRODUCTION

Iodine-123-N-isopropyl-p-iodoamphetamine (IMP) and single photon emission computed tomography (SPECT) have been used for the quantitative measurement of regional cerebral blood flow (rCBF) according to the microsphere (MS) model[1–3] or two-compartment model[4–7] analysis. Because of a linear relationship between IMP uptake and blood flow in regional brain tissues and the favorable chemical properties of IMP in SPECT acquisition and determining the concentration of IMP in blood, these methods proved to provide reliable rCBF values. Recently several simplified methods have been reported,[8–10] but these methods still require arterial blood sampling (ABS) which is invasive and demanding in a daily clinical setting.

A recent report suggested that rCBF could be calculated with IMP and SPECT without any blood sampling.[11] The method uses a planar dynamic scan of the chest for 3 minutes after an injection of IMP to estimate cardiac output and the integral of the input function (see Theory). The method is theoretically promising but a validation study is needed before routine clinical use. In this study, we tested the method in a group of patients with a variety of neurological disorders by comparing the input function and rCBF estimated by the method with those obtained by using a two-compartment model analysis of dynamic SPECT and ABS data.

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MATERIALS AND METHODS

Theory

According to the microsphere model, rCBF (m*l*/g/min) is calculated as follows,

$$rCBF = Cb(T)/\int_0^T Ca(t)dt \quad (1)$$

where Cb(T) (μCi/g) is regional radioactivity of the brain tissue at T minutes after an injection of the tracer, and Ca(t) (μCi/m*l*) is the radioactivity-time course of the tracer in arterial blood. If cardiac output (CO: m*l*/min) and the total amount of tracer delivered to the whole body in T minutes (TC(T): μCi) are known, $\int_0^T Ca(t)dt$ (min$*\mu$Ci/m*l*) can be replaced by TC(T)/CO (min$*\mu$Ci/m*l*).

The cerebral perfusion tracer, IMP, is known to accumulate in the lungs after an intravenous injection and is gradually released from the lungs into the systemic circulation. As a chemical microspheric substance, a lipophilic portion of IMP goes into the brain and is retained without significant loss from the brain, at least for several minutes after an injection. Assuming that peak counts of the lung represent the injected dose and re-circulation of the tracer is negligible in T minutes, TC(T) is replaced by an injected dose (D: μCi) multiplied by the ratio of clearance from the lung in T minutes (R(T)) and a mean lipophilic fraction of IMP (Fr) as follows,

$$TC(T) = D*R(T)*Fr. \quad (2)$$

From the peak activity of the lung (Lpeak) and activity of the lung at T minutes (L(T)), R(T) is calculated as follows,

$$R(T) = (Lpeak - L(T))/Lpeak. \quad (3)$$

Cardiac output can be estimated from first pass data for the right heart or pulmonary artery trunk of a chest dynamic scan after an injection of IMP.[11,12] Therefore, rCBF can be calculated non-invasively by using the microsphere model with IMP as follows,

$$rCBF = Cb(T)/(TC(T)/CO) = Cb(T)*CO/(D*R(T)*Fr). \quad (4)$$

Subjects

Forty-five patients (age: 59.1 ± 15.4, male/female: 36/9) with a variety of neurological disorders were included in this study (Tables 1a and 1b). As nine patients were studied twice and two were studied three times before and after therapeutic procedures or during the course of clinical follow-up, fifty-eight studies were included in this study. During the study, frequent ABS was performed in all patients. We divided the 58 studies into 2 groups. The first 28 studies in 23 patients (age: 56.7 ± 17.7, male/female: 17/6) were analyzed in comparison with ABS data to derive equations for correction yielding an accurate input function from the chest dynamic scan data (first group, Table 1a). The subsequent 30 studies in 22 patients (age: 61.6 ± 12.4, male/female: 19/3) served to confirm the validity of the proposed method with the equations for

Table 1a Demographics of patients in the first group

case No.	age	sex	Diag.	No. of exam.
1	22	m	CCF	1
2	64	m	lt VA stenosis	1
3	50	f	Moyamoya dis.	1
4	56	f	CCF	1
5	66	m	rt ICA occlusion	3
6	75	m	lt ICA stenosis	1
7	69	m	lt VA occlusion	1
8	65	f	CCF	1
9	22	m	AVM	1
10	69	m	rt ICA stenosis	1
11	72	f	rt ICA stenosis	1
12	70	m	rt ICA stenosis	1
13	25	f	Aortitis	1
14	67	m	AVF	1
15	72	m	rt ICA occlusion	1
16	72	m	rt ICA occlusion lt ICA stenosis	2
17	60	f	AVF	1
18	59	m	rt MCA stenosis	2
19	63	m	lt ICA occlusion rt ICA occlusion	1
20	42	m	AVM	2
21	25	m	Moyamoya dis.	1
22	72	m	bil MCA stenosis	1
23	47	m	rt SA stenosis	1

SA: subclavian artery

Table 1b Demographics of patients in the second group

case No.	age	sex	Diag.	No. of exam.
1	73	f	CCF	1
2	57	f	rt MCA stenosis	1
3	60	m	rt ICA stenosis lt MCA stenosis	1
4	71	m	rt ICA occlusion	1
5	63	m	lt MCA stenosis	1
6	76	m	cerebral infarction	1
7	76	m	rt ICA stenosis lt MCA stenosis	1
8	43	m	lt ICA stenosis	1
9	70	m	bil ICA stenosis	2
10	61	m	rt ICA occlusion lt ICA stenosis	3
11	75	m	bil ICA stenosis	1
12	65	m	rt ICA occlusion	2
13	65	m	lt ICA occlusion rt ICA stenosis	2
14	45	m	bil SA occlusion	2
15	52	m	lt ICA stenosis	2
16	35	m	rt ICA occlusion	1
17	52	m	MCA aneurysm	1
18	72	m	bil ICA stenosis	2
19	65	m	bil CCA stenosis	1
20	44	f	bil MCA stenosis	1
21	56	m	rt ICA stenosis	1
22	80	m	AVF	1

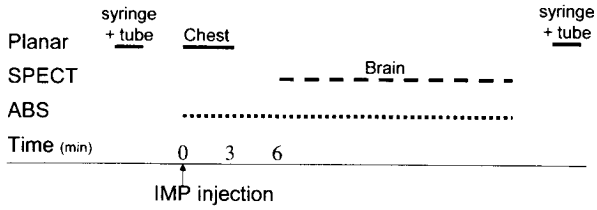

Fig. 1 The procedure of the method is shown. Arterial blood sampling (ABS) was frequently done during the scan in all patients. Positioning of the patient's head for the brain SPECT was done immediately after the end of the chest scan.

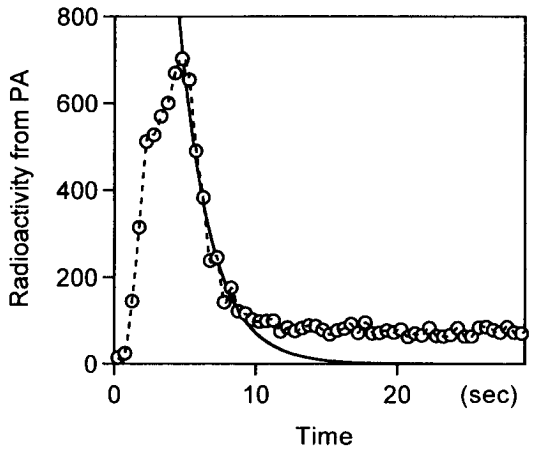

Fig. 2 A time-activity curve from the pulmonary artery trunk during the first pass phase is shown. A least squares exponential fit to the downward slope of the curve (solid line) was performed to calculate the area under the curve.

correction (second group, Table 1b).

The study was performed according to the guidelines of the ethical committee of Kyoto University Hospital for human studies, and all subjects gave informed consent.

General procedure

We used a three-head SPECT scanner (PRISM3000, Picker Int. Ohio) equipped with a low energy general purpose collimator. Patients underwent a dynamic planar scan of the chest with one of the detectors for 3 minutes (0.5 sec/frame, 7.1 × 7.1 mm/pixel, 64 × 64 matrix) followed by a dynamic SPECT scan of the brain for 20 minutes (1 min/frame) after a bolus injection of IMP (Fig. 1). Twenty 1-minute raw data were reconstructed to ten 2-minute SPECT frames (3.4 × 3.4 mm/pixel with 14.2 mm in thickness, 64 × 64 matrix) by a filtered back-projection method with a Butterworth filter. One 10-minute SPECT frame from about 10 to 20 minutes after an injection was also reconstructed for subjects in the second group. Details of performance of the scanner and image reconstruction procedures were reported previously.[6]

We loaded IMP (111–167 MBq in 1–1.5 m*l*) in an extension tube (volume 3.8 m*l*) connected to a 10-m*l* syringe in advance and injected it as a bolus into the antecubital vein in 5 seconds with 10 m*l* of saline. Radioactivity in a syringe and extension tube was measured before and after an injection by means of the scanner in all studies and by means of a dose calibrator in 39 studies to confirm the dose which entered the body. For measurement with the scanner, the distance between the surface of the collimator and the syringe containing the tracer was set at 10 cm in all studies. Because radioactivity measured with the scanner agreed well with that measured with a dose calibrator, with the mean and SD of differences between two measurements being 1.0% and 3.9%, respectively, we measured an injected dose (D in Eq. 2) by means of the scanner only in the rest of the studies.

Data acquisition for the brain was started about 6 minutes after an injection of IMP (mean ± SD: 6.06 ± 0.93 minutes in the first group and 5.66 ± 0.61 minutes in the second group, no significant difference between the two groups). During scans, nineteen arterial blood samples were taken through a small catheter inserted into the radial artery (every 5 seconds from 10 to 50 seconds, at 60, 75, 90, 120 and 150 seconds, and at 3, 5, 10, 20 and 30 minutes after an injection).

Estimation of cardiac output

First pass data for the pulmonary artery trunk on a chest dynamic scan were used to estimate CO.[11,12] This procedure was a modified version of the established procedure for measuring CO with a Tc-99m-labeled blood pool tracer.[13,14] Briefly, applying the concept of the Stewart-Hamilton principle, the index of CO (COI) is calculated as follows,

$$COI = Dc/(B/A) \quad (5)$$

where Dc (counts/min) is an injected dose counted by means of a gamma camera for one minute, A (cm^2) is the area of a ROI placed on the pulmonary artery trunk and B (counts) is the area under a time-activity curve from the ROI. A rectangular ROI 14.2 × 14.2 mm in size was used as A. A least squares exponential fit to a downward slope of the curve was performed to calculate B[13] (Fig. 2). COI (unit: cm^2/min) was converted to CO (liter/min) according to an equation which was derived from a relationship between COI and CO measured by the cardiac echo Doppler method.[12] Accuracy and reproducibility of CO measurement by the cardiac echo Doppler method have been well validated.[15,16] The equation used for conversion from COI to CO in this study was as follows,

$$CO = 2.29*(COI)^{0.634}. \quad (6)$$

Estimation of an input function from a lung curve

To estimate an accurate TC(T) from a lung washout curve for 3 minutes, we analyzed the washout curve in comparison with ABS data in the first group of 28 studies. Two large ROIs covering both lung fields were drawn to obtain a curve for washout of the tracer from the lungs (Fig. 3). The washout ratio in 3 minutes (R(3)) was defined as (Lpeak – L(3))/Lpeak (L(3): radioactivity in the lungs at

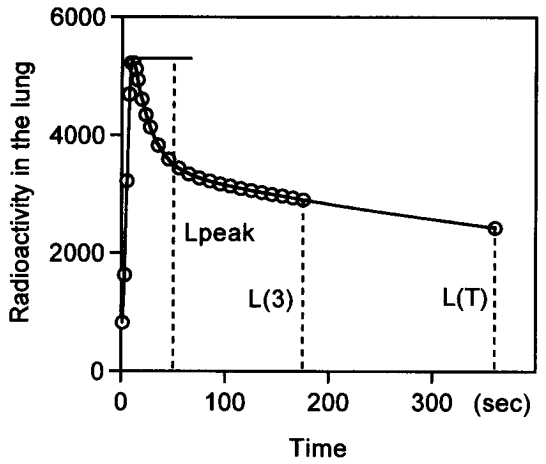

Fig. 3 A lung washout curve is shown. The washout ratio at 3 minutes after an injection (R(3)) was defined as (Lpeak – L(3))/ Lpeak. An extrapolated lung washout curve was used to determined radioactivity remained in the lung at T minutes (L(T)).

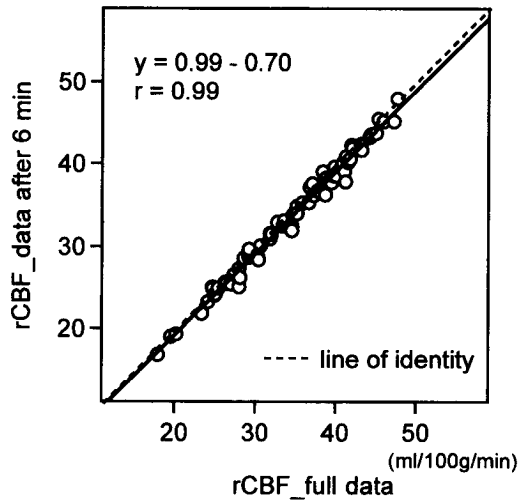

Fig. 4 A plot of rCBF estimated using data without first 6 minutes against those estimated by using a full data set in 35 patients is shown. Data points were almost on a single line close to the line of identity. The mean and SD of differences between these two rCBFs were −1.0 and 0.8 ml/100 g/min, respectively, confirming good agreement.

3 minutes after an injection). As a first step, to test assumptions described in the theory that peak counts for the lungs represented an injected dose and re-circulation of the tracer was negligible, we compared R(3) with the corresponding value calculated with CO, D and ABS data. Through this comparison, we derived an equation for correction yielding more accurate R′(3) from R(3). In the second step, we compared two procedures to estimate the washout ratio in T minutes (R′(T)) from R′(3). In the first procedure we used an extrapolated lung washout curve (R(t)) obtained by fitting a downward slope of the curve with a two-exponential curve (therefore, R′(T) = R′(3)*(R(T)/R(3)). In the second procedure, we estimated R′(T) from R′(3) multiplied by a population mean of $\int_0^T Ca(T)dt/\int_0^3 Ca(T)dt$ (standard ratio: SR(T)), which was calculated by using the data from the first 28 subjects (therefore, R′(T) = SR(T)*R′(3)). Ratios of R′(T) to R′(3) obtained through these procedures were compared to individual $\int_0^T Ca(T)dt/\int_0^3 Ca(T)dt$ obtained by using ABS data.

Determination of cerebral blood flow

Four large regions of interest (ROIs) were manually drawn for each patient. One ROI covered the whole brain and two ROIs included large cortical areas of each cerebral hemisphere in a slice of the corona radiata and lateral ventricles. The forth ROI was set on the cerebellum. The ROI covering the whole brain was used to calculate mean CBF (mCBF-test) by using data from the chest dynamic scan and the first frame of the dynamic SPECT scan as follows,

$$\text{mCBF-test} = Cwb(T)*CO/(D*R'(T)*Fr) \qquad (7)$$

where Cwb(T) is total radioactivity in the brain in one image slice. Then, to reduce statistical noise, regional values for CBF (rCBF-test) were calculated on 10-minute SPECT images by redistributing the value for mCBF-test according to ratios of regional to total radioactivity of the brain.

A two-compartment model analysis of the dynamic SPECT and ABS data was used to determine CBF in the four ROIs used as references (mCBF-ref for the whole brain CBF and rCBF-ref for regional CBF). Because the dynamic SPECT in this study lacked data for first 5–6 minutes, we confirmed that rCBF determined with SPECT data lacking for the first 6 minutes agreed well with rCBF determined with a full data set in another group of 35 patients (Fig. 4). We used 0.75 for a lipophilic fraction of IMP in the calculation of mCBF-test, whereas a standard time-course of a lipophilic fraction of IMP previously determined in 20 subjects was used for ABS data in the two-compartment model analysis.

Evaluation of the method

The validity of the proposed method was evaluated in the second group of 30 studies. The reliability and reproducibility were assessed by using the mean and SD of differences in obtained values between two methods or between two studies.[17] Linear regression analyses were also performed to correlate obtained values between two methods or between two studies. To exemplify the reliability of the method in a wide range of CBF, we made a comparison of rCBF-test and rCBF-ref, which were obtained from regions with high CBF (normal cortex and cerebellum) and low CBF (ischemic cortex). The reproducibility of the method was assessed by seeing the stability and/or alteration of CO, R′(3) and rCBF-test in thirteen pairs of two consecutive studies. Because CO and R′(3) did not seem

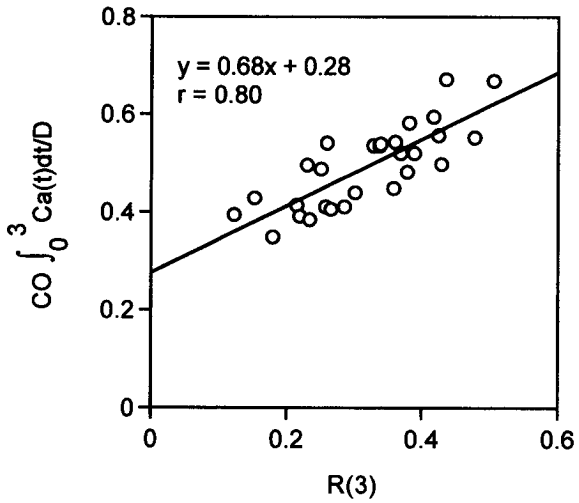

Fig. 5 A plot of $CO*\int_0^3 Ca(t)dt/D$ against R(3) showed a linear relationship between them ($y = 0.68x + 0.28$, $r = 0.80$), although R(3) was constantly smaller than $CO*\int_0^3 Ca(t)dt/D$. To estimate a more accurate $CO*\int_0^T Ca(t)dt/D$ from R(3), the equation for linear regression was used in the further analysis.

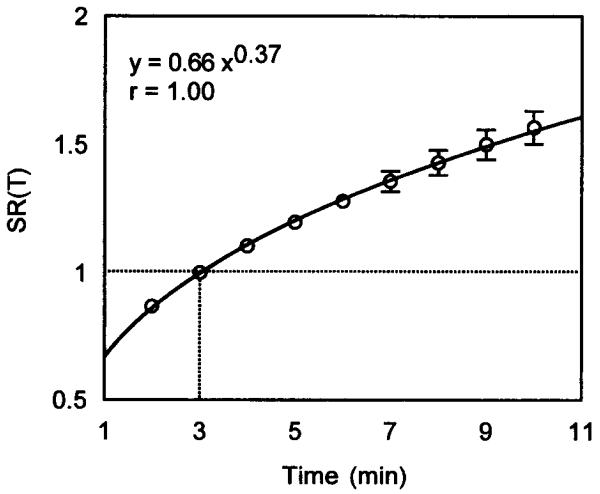

Fig. 6 A time-course of standard ratios $\left(SR(T) = \int_0^T Ca(t)dt / \int_0^3 Ca(t)dt\right)$ obtained from the ABS data in the first group of 28 subjects is shown with error bars (± SD). The variation among patients at each time point was small with the coefficient of variation being 1.9% at 5 minutes and 2.9% at 7 minutes after an injection.

to be affected by therapeutic procedures for the brain, we compared CO and R′(3) in two studies. Regarding rCBF, there might be a difference between two studies because nine out of 11 patients underwent cerebral revascularization surgery. We, therefore, compared changes in the rCBF-test from the first to the second study with those of rCBF-ref. Thirteen consecutive studies were available in 11 patients, and two cortical ROIs in each patient were used for the analysis.

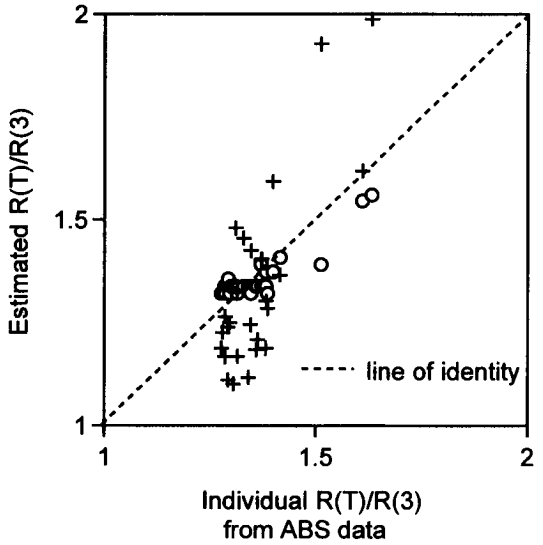

Fig. 7 Estimated ratios of R(T) to R(3) obtained from extrapolated lung curves (+) and standard ratios (○) in the first group were plotted against individually calculated $\int_0^T Ca(t)dt/\int_0^3 Ca(t)dt$ obtained by using the ABS data. Although estimated ratios from standard ratios agreed well with individually calculated ratios using the ABS data, estimated ratios from extrapolated lung curves did not.

RESULTS

In the 28 studies of the first group, CO was in a physiological range between 3.78 and 5.74 liter/min (mean ± SD: 4.62 ± 0.49), R(3) between 0.12 and 0.50 (0.32 ± 0.10) and mCBF-ref between 16.8 and 40.5 ml/100 g/min (27.5 ± 6.7). Because R(3) was linearly correlated with, but constantly smaller than, a corresponding value, $CO*\int_0^3 Ca(T)dt/D$ (Fig. 5), we defined R′(3) as follows,

$$R'(3) = 0.690*R(3) + 0.289. \quad (8)$$

The standard ratio of $\int_0^T Ca(T)dt$ to $\int_0^3 Ca(T)dt$ (SR(T)) obtained from ABS data in the first group was expressed as follows (Fig. 6),

$$SR(T) = 0.660*T^{0.372}. \quad (9)$$

Variations in SR(T) were small, especially within 10 minutes after an injection (coefficient of variation at 7 minutes: 2.9%), and SR(T) represented the individual $\int_0^T Ca(T)dt/\int_0^3 Ca(T)dt$ better than that obtained from the extrapolated lung curve (Fig. 7). Therefore, the final equation to calculate mCBF-test was determined as follows,

$$\text{mCBF-test} = CO*Cwb(T)/ (D*(0.660*T^{0.372}) *(0.690*R(3) + 0.289)*Fr). \quad (10)$$

In the 30 studies of the second group, CO ranged between 3.63 and 7.55 liter/min (mean ± SD: 5.24 ± 0.81), R(3) between 0.14 and 0.49 (0.34 ± 0.10) and mCBF-ref

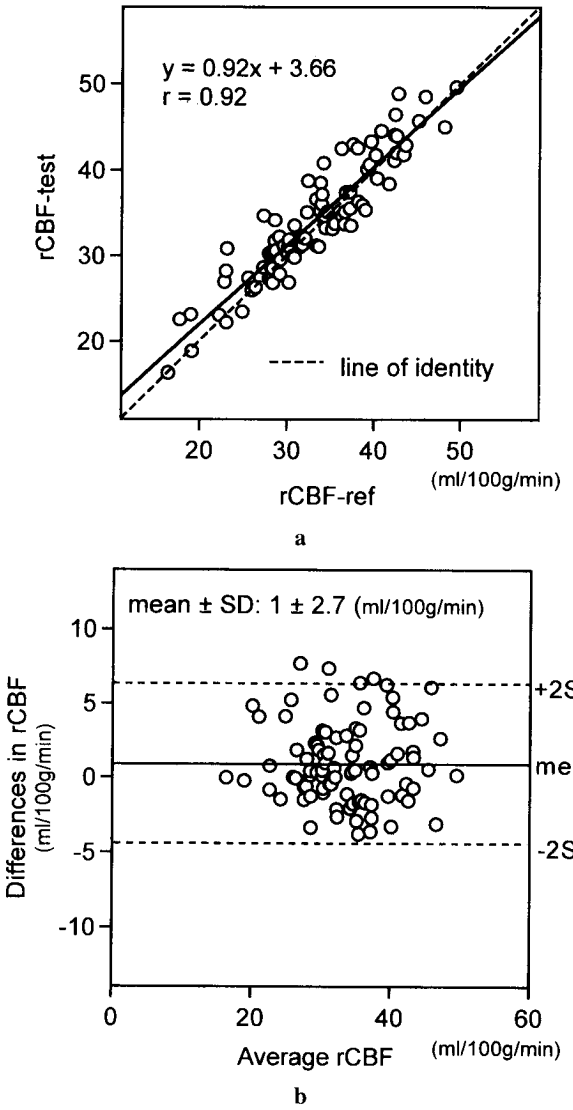

Fig. 8 (a) A plot of rCBF-test against rCBF-ref in the second group is shown. A linear relationship was noted between rCBF-test and rCBF-ref and all data points were seen around a line of identity. (b) Differences between rCBF-test and rCBF-ref were plotted against the averaged values of these rCBFs. rCBF-test agreed well with rCBF-ref with the mean and SD of differences being 1.0 and 2.7 ml/100 g/min.

between 18.1 and 37.8 ml/100 g/min (28.2 ± 5.3). There was a significant difference in CO ($p < 0.01$), but not in R(3) and mCBF-ref, between the first and second groups. When Eq. 10 was applied to this group, the rCBF-test correlated and agreed well with rCBF-ref, showing a correlation coefficient of 0.92 (Fig. 8a) and the mean and SD of differences between rCBF-test and rCBF-ref of 1.0 and 2.7 ml/100 g/min, respectively (Fig. 8b).

In patients who underwent more than two studies on separate days, percentage changes in rCBF-test between the two consecutive studies showed a linear relationship with those in rCBF-ref (Fig. 9). The mean and SD of

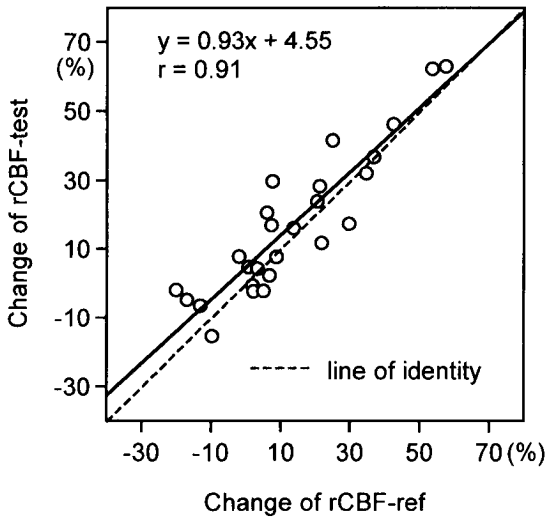

Fig. 9 Changes in rCBF-test from the first to the second measurement on separate days expressed as a percentage correlated well with those in rCBF-ref. An increase or decrease in rCBF-ref from the first to the second measurement was well represented by rCBF-test.

differences between changes in rCBF-test and rCBF-ref were 3.6 and 8.8%, respectively. The mean and SD of differences between the two consecutive studies were 0.33 (6.3%) and 0.86 (16.5%) liter in CO, and 0.001 (0.1%) and 0.031 (7.1%) in R′(3), respectively.

DISCUSSION

In this report we demonstrated that rCBF could be calculated by using IMP and SPECT without any blood sampling by adding a chest dynamic scan for 3 minutes after an injection of IMP. But assumptions referred to in the theory, that peak counts of the lung represented the injected dose and that re-circulation of the tracer was negligible for several minutes, did not seem to be valid in our procedures. The input function obtained from dynamic chest scan data was systematically smaller than the input function obtained from ABS data. It is well known that smokers have slow washout of IMP from the lung.[18] Peak counts of the lung would be affected by how rapidly the tracer was given as a bolus. Photon attenuation by the chest wall and/or a partial volume effect may result in errors in the estimation of CO. The equation for conversion from COI to CO was derived from the comparison with the cardiac echo Doppler method.[12] Therefore, errors in the cardiac echo Doppler method may propagate, eventhough the accuracy and reproducibility of the method have been validated.[15,16] There are many factors that cause errors in estimating the input function and it seems difficult to analyze each of them. Therefore, we found a practical solution. We derived two equations from the first group of patients to correct an input function obtained

from the lung washout curve by analyzing with ABS data. These equations worked well in the second group of patients that was independent of the first group, indicating the validity of the methods with these equations for correction in the general population.

The mean and SD of differences between rCBF-test and rCBF-ref were 1.0 and 2.7 ml/100 g/min (3.2 and 8.4%, respectively, when expressed as a percentage), indicating that the reliability was in an acceptable range as a method without any blood sampling. Okubo et al.[19] evaluated the accuracy and reliability of several simplified methods for quantifying rCBF by using IMP and SPECT. They compared rCBF obtained with those simplified methods with that obtained by means of a nonlinear least squares fitting (NLLSF) method based on a two-compartment model analysis, that was the same as that used in this study. Their results showed a mean error of 6.8% when the microsphere model with continuous ABS was used and 10.4% when the microsphere model with a standard input function calibrated with an arterial blood sample at a single time point. Although they did not show a definition of the mean error, it was probably an average of absolute differences expressed as a percentage between the rCBF tested and rCBF obtained by means of the NLLSF method divided by rCBF obtained by means of the NLLSF method. We obtained a mean error of 7.0% in this study when calculated in this way, and value was comparable with theirs. Therefore, our method seems to be sufficiently reliable as a method without any blood sampling and acceptable for clinical application.

We could not evaluate the reproducibility of the method in the test-retest conditions in our clinical study but we compared the CO and R′(3) for the two studies, because CO and R′(3) did not seem to be affected by therapeutic procedures for the brain. Although CO was not well reproduced in some patients, it may have varied due to physical and mental stress during the study, especially at the time of the injection. Compared with CO, R′(3) was well reproduced with an acceptably small SD of differences (7.1%). The reproducibility of the rCBF-test may be difficult to assess because nine of 11 patients received a revascularization procedure between the two studies but we found a linear relationship between changes in the rCBF-test and rCBF-ref between the first and second studies. An increase or decrease in the rCBF-ref after therapeutic procedures was well represented by the rCBF-test and the change in the rCBF-test was small in patients without a significant change in the rCBF-ref.

rCBF values calculated by the proposed method were considerably lower than generally accepted rCBF values,[20] but were comparable to the reported rCBF values obtained with IMP and SPECT[6–8,19,21] and those obtained by means of a two-compartment model analysis of dynamic SPECT and ABS data in this study. This underestimation of rCBF can be mainly attributable to the limited spatial resolution of the SPECT scanner and the limited extraction fraction of IMP as suggested previously.[7–9,20] As shown by the reliability and reproducibility in this study, the method seems to be sufficiently acceptable for clinical use. Although the measurement of rCBF may not be necessary for many patients, it is informative for management of patients with cerebrovascular diseases, especially those with an occlusive disease of the cerebral major artery, by revealing the magnitude of ischemia, monitoring response to therapy and predicting the outcome.[21] This noninvasive method that can be performed in usual clinical settings is widely applicable and beneficial for patients.

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