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Quantifying regional cerebral blood flow with N-isopropyl-p[^{123}I]iodoamphetamine by ring-type single-photon emission computed tomography: Validity of a method to estimate early reference value by means of regional brain time-activity curve

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A more accurate quantitative method for the measurement of regional cerebral blood flow (rCBF) with the microsphere model and N-isopropyl-p-[^{123}I]iodoamphetamine (^{123}I-IMP) and ring-type single-photon emission computed tomography (SPECT) was developed. Continuous withdrawal of arterial blood was carried out for 5 minutes after the injection. Static SPECT data were acquired from 25 min to 55 min. To estimate reconstructed images at 5 min, total brain count collections and one minute SPECT studies were performed at 5, 20, and 60 min. Quantitative values for rCBF were calculated from short time SPECT images at 5 min (rCBF), static SPECT images corrected by total brain counts ($rCBF_{Ct}$) and those corrected by reconstructed counts on short time SPECT images ($rCBF_{Cb}$). Practically, $rCBF_{Cb}$ is calculated by using reconstructed counts of regions of interest placed in the same position as static SPECT and short time SPECT at 5, 20, 60 min. Although there was good correlation between rCBF and $rCBF_{Ct}$ ($r = 0.69$), $rCBF_{Ct}$ tended to be underestimated in high flow areas and overestimated in low flow areas. A better correlation was observed between rCBF and $rCBF_{Cb}$ ($r = 0.92$). The overestimation and underestimation observed in $rCBF_{Ct}$ was considered to be due to the correction method with a total cerebral time activity curve, because the kinetic behavior of ^{123}I-IMP was different in each region.

Key words: ^{123}I-IMP, single photon emission computed tomography, rCBF measurement, microsphere model, distribution volume

INTRODUCTION

SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY (SPECT) has been applied increasingly to the study of normal and pathologic states. N-isopropyl-p-[^{123}I]iodoamphetamine (^{123}I-IMP) was proposed as a tracer for the measurement of regional cerebral blood flow (rCBF). Since the tracer has high first-pass extraction and subsequent retention in the brain, the initial regional distribution of ^{123}I-IMP is considered to represent rCBF.[1,2] Kuhl et al.[3] reported the validity of the microsphere model for quantitative mapping of rCBF by SPECT with intravenously injected ^{123}I-IMP. SPECT studies with a rotating gamma camera system are usually performed at the time when brain activity reaches a plateau. To estimate early reference values for rCBF with a rotating gamma camera, it is necessary to correct the obtained tomographic images. The correction is usually performed by means of total brain time-activity curve.[4] The kinetic behavior of ^{123}I-IMP in each region is different.[5] Total brain time-activity curve does not therefore reflect the temporal change in activity in each region.

The purpose of this study is to evaluate the influence of the correction methods on estimating early reference values, and to develop a more accurate quantitative measurement of rCBF.

MATERIALS AND METHODS

Phantom experiments

To evaluate the accuracy of reconstructed counts of short time SPECT, phantom studies were performed. One minute or five minutes short time SPECT and static SPECT were

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Table 1 The conditions for the SPECT of the brain phantom

	Static SPECT	Short time SPECT			
Data acquisition time (min)	30	5	5	1	1
Matrix size	128 × 128	128 × 128	64 × 64	128 × 128	64 × 64
Cut-off frequency (mm)	18	18	30	18	30
Order	4	4	4	4	4
Axial resolution (mm in FWHM)	13.0	13.0	19.8	13.0	19.8

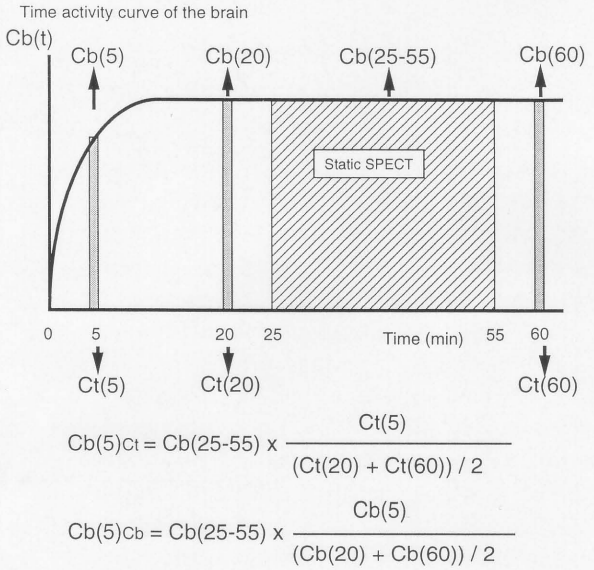


Fig. 1 Time schedule of this study. To estimate reconstructed counts at 5 min, total brain count collections were performed at 5 min, 20 min, and 60 min. Short time SPECT images were reconstructed with these data. Static SPECT data were collected from 25 to 55 min after tracer injection. Ct(t): total brain count at t min. Cb(t): reconstructed counts at t min.

performed under various conditions (Table 1). SPECT images were obtained with a ring-type SPECT system (HEADTOME SET-050, Shimadzu, Japan) equipped with a high resolution (HR) collimator. A 20-cm cylindrical phantom filled with ^{123}I-IMP solution was scanned under each condition. The ^{123}I-IMP solution was prepared as 12.4 MBq/*l*. A 120 × 120 mm square region of interest (ROI) was placed on each reconstructed image. The reconstructed count for each ROI was measured, and coefficients of variation (C.V.) for the various conditions were compared.

Patient selection

Seventeen patients with various brain diseases were studied, including 6 males and 11 females, aged from 19 to 74 yr (average: 54.2 yr). Brain diseases included 3 cerebral infarction, 4 transient ischemic attack, 2 epilepsy, 2 Alzheimer disease, 1 each of cerebral hemorrhage, spinocerebellar degeneration, progressive supranuclear palsy, carotid-cavernous fistula, A-V malformation, and aneurysm of the basilar artery. All patients were examined in the stable stage. None of them had a respiratory or heart disease.

Data acquisition

With the patient recumbent on the couch, the head was positioned with the orbitomeatal plane parallel to the plane of tomography. A dose of 222 MBq (6 mCi) of ^{123}I-IMP was injected intravenously as a bolus. Prior to the ^{123}I-IMP injection, an indwelling catheter was inserted into a radial artery. Immediately after the injection, continuous arterial blood withdrawal with a Harvard infusion-withdrawal pump was performed at a constant rate of 1 ml/min for 5 minutes. Static SPECT data were acquired from 25 to 55 min after tracer injection, when brain activity reached a plateau. Total brain count collections for one minute were performed at 5, 20, and 60 min, and short time SPECT images were reconstructed with these data. Total brain count at t min was represented as Ct(t). Reconstructed counts at t were described as Cb(t) (Fig. 1).

All SPECT images were reconstructed by means of filtered backprojection with a Ramp and Butterworth filter. The cut-off frequency and order of short time SPECT were 30 mm and 4, those of static SPECT were 18 mm and 4. Attenuation correction was made numerically by assuming an elliptical brain outline.[6] Ten transaxial sections of static SPECT image 10 mm thick were reconstructed on 128 × 128 matrices. The same level short time SPECT images of the same thickness were reconstructed on 64 × 64 matrices, and then they were changed to 128 × 128 matrices. The axial resolutions for one minute short time SPECT image and static SPECT image were 19.8 mm and 13.0 mm in full width at half maximum, respectively.

Cross calibration of the short time SPECT images, the static SPECT images and the radioactivity in the arterial blood samples, measured with the well counter, was performed with scanning a 16 cm diameter cylindrical phantom filled with ^{123}I-IMP solution.

Analysis

Regional CBF was calculated by an arterial blood

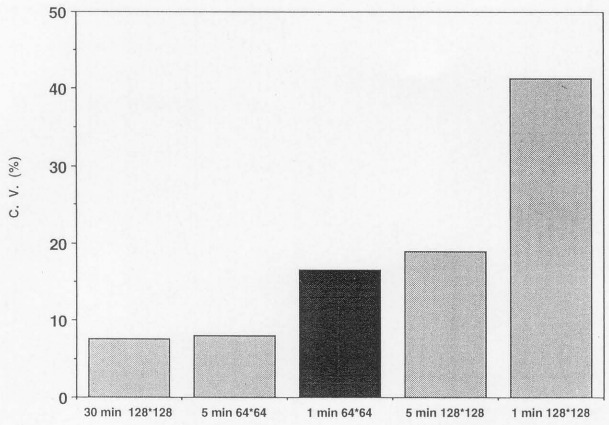


Fig. 2 Coefficient of variation (C.V.) of the reconstructed counts of ROI. The minutes mean data acquisition time, and the numbers mean matrix sizes of the phantom SPECT images.

sampling method with the microsphere model as follow:

$$F = R \times Cb/(N \times A) \quad (1)$$

where F is the cerebral blood flow in milliliters per 1 gram per minute, R is the constant withdrawal rate for arterial blood, which was actually 1 ml/min, and Cb is the brain activity concentration derived from the SPECT images, which were adjusted to the counts per minute by cross calibration factors measured by a well-scintillation counter. A is the total activity of arterial whole blood withdrawn from 0 to 5 min, and N is the fraction of A, representing true tracer activity. N was determined by counting octanol extraction of the reference arterial blood sample.

Regional CBF with short time SPECT images at 5 min were calculated as follows:

$$rCBF = Cb(5)/(N \times A) \quad (2)$$

Static SPECT images were obtained from 25 min to 55 min. These images were corrected by the reference value for total brain counts, as Ct(5), Ct(20) and Ct(60), or by reconstructed counts, as Cb(5), Cb(20) and Cb(60). Practically, Cb(t) was obtained by measuring the counts of ROI settled at the same position on static SPECT and short time SPECT images at 5, 20, and 60 min. The reference value at 5 min was described as follows:

$$Cb(5)_{Ct} = Cb(25\text{–}55) \times \frac{Ct(5)}{(Ct(20) + Ct(60))/2} \quad (3)$$

$$Cb(5)_{Cb} = Cb(25\text{–}55) \times \frac{Cb(5)}{(Cb(20) + Cb(60))/2} \quad (4)$$

$Cb(5)_{Ct}$ and $Cb(5)_{Cb}$ are the corrected counts at 5 min obtained with total brain counts and those with reconstructed counts for short time SPECT images, respectively. Cb(25–55) is the cerebral activity from 25 to 55 min after injection derived from the static SPECT images (Fig. 1).

According to formulae (1), (3) and (4), rCBF obtained by means of static SPECT can be described as follows:

$$rCBF_{Ct} = Cb(5)_{Ct}/(N \times A) \quad (5)$$

$$rCBF_{Cb} = Cb(5)_{Cb}/(N \times A) \quad (6)$$

where $rCBF_{Ct}$ and $rCBF_{Cb}$ are the rCBF calculated from static SPECT images corrected with total brain counts and reconstructed counts for each ROI on the short time SPECT images, respectively.

When measuring the rCBF, 12 × 12 mm square ROIs on each SPECT image were selected. Three ROIs were placed in the frontal cortex of each hemisphere, two in the occipital cortex, the temporal cortex, and the parietal cortex. Anatomical identification of each position was confirmed by superimposition of the SPECT films on the X-CT films that were taken at the same levels as the SPECT images.

Arterial pCO_2 was measured at 0, 10, 20, and 40 minutes, and it was confirmed that there was no significant change.

RESULTS

Phantom experiments

Figure 2 shows the C.V. of reconstructed counts for each condition. The C.V. of one minute SPECT images reconstructed on 64 × 64 matrices was approximately the same as that of 5 minutes SPECT images reconstructed on 128 × 128 matrices. It was smaller than that of one minute SPECT images reconstructed on 128 × 128 matrices.

Clinical experiments

Figure 3 shows the rCBF images for each procedure.

In 17 patients with various brain diseases, rCBF, $rCBF_{Ct}$, and $rCBF_{Cb}$ in gray matter ranged from 20.3 to 76.7 (mean ± SD: 48.0 ± 10.5) ml/100 g/min, from 19.2 to 75.4 (mean ± SD: 56.5 ± 9.5) ml/100 g/min, and from 18.6 to 81.3 (mean ± SD: 51.7 ± 11.9) ml/100 g/min, respectively. Figure 4 shows the relationship between rCBF and $rCBF_{Ct}$. Although a significant correlation (r = 0.69) was observed, $rCBF_{Ct}$ was overestimated in the low flow areas, and underestimated in the high flow areas. The closed circles represent evident pathologic lesions shown as low density on X-CT (e.g., infarction). In the pathologic lesions, $rCBF_{Ct}$ were plotted closer to the rCBF value. The relationship between rCBF and $rCBF_{Cb}$ (Fig. 5) shows a better correlation (r = 0.92). No overestimation or underestimation was observed.

DISCUSSION

It has been reported that the rCBF value with ^{123}I-IMP and the microsphere model correlates well with rCBF measured by ^{133}Xe inhalation SPECT.[7,8] The microsphere model holds true under the assumptions that the tracer is com-

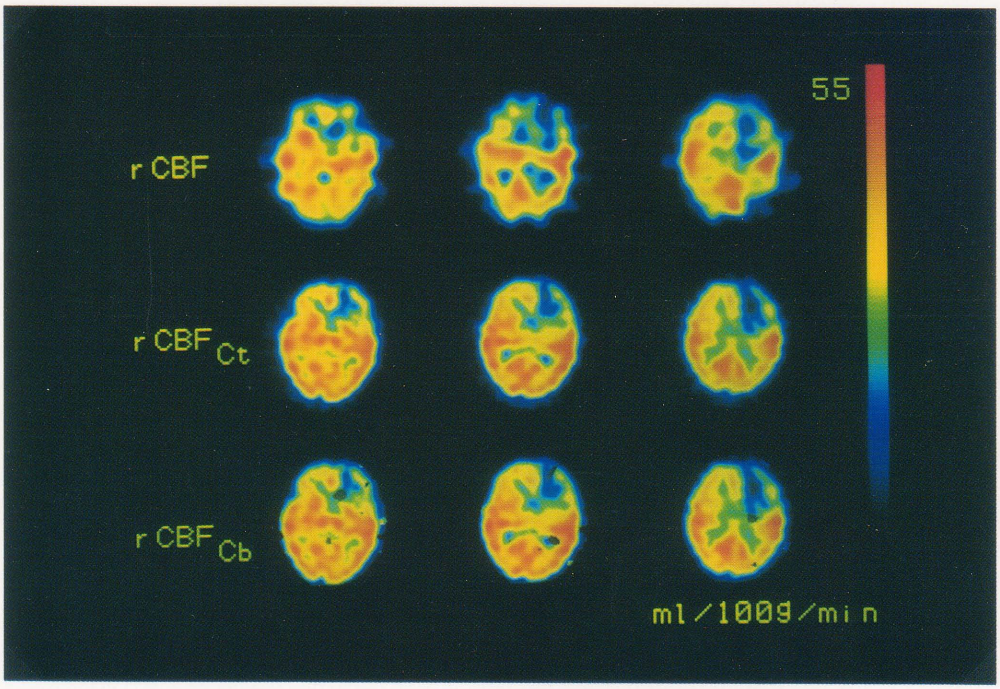


Fig. 3 Regional CBF images for each procedure. A 61 year-old female with cerebral hemorrhage. rCBF: rCBF images obtained from short time SPECT at 5 min. $rCBF_{Ct}$: rCBF images obtained from static SPECT corrected by total brain counts. $rCBF_{Cb}$: rCBF images obtained from static SPECT corrected by each reconstructed counts for ROI. The numbers show rCBF value (ml/100 g/min).

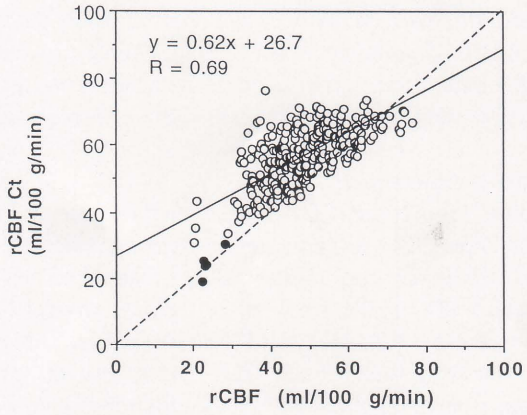


Fig. 4 Relationship between rCBF (ml/100 g/min) and $rCBF_{Ct}$ (ml/100 g/min). rCBF: rCBF obtained from short time SPECT at 5 min. $rCBF_{Ct}$: rCBF obtained from static SPECT corrected by total brain counts. The closed circles represent evident pathologic lesions (e.g., infarction), which were shown on X-CT.

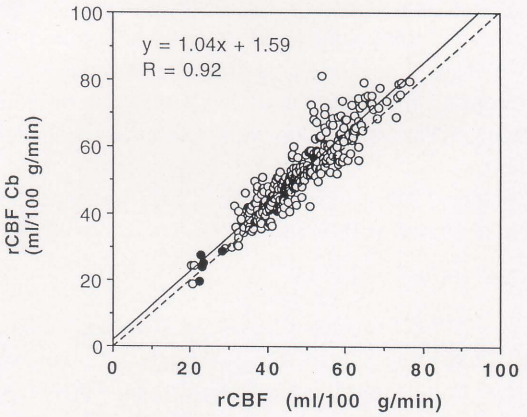
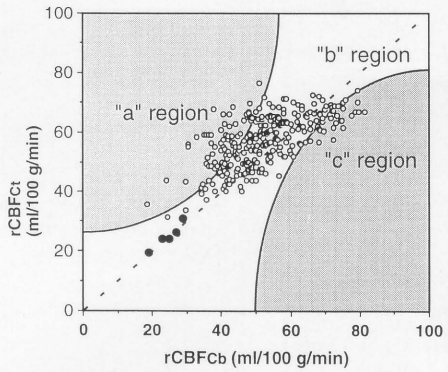


Fig. 5 Relationship between rCBF (ml/100 g/min) and $rCBF_{Cb}$ (ml/100 g/min). $rCBF_{Cb}$: rCBF obtained from static SPECT corrected by each reconstructed counts for ROI.

pletely removed on a single pass through the brain and the back-diffusion from brain to blood can be neglected. Practically, ^{123}I-IMP is almost completely removed on a single pass, and its back-diffusion is negligible at a sufficiently early time (e.g., for 5 min after injection).[3,11,12] With the passing of time, its back-diffusion becomes no longer negligible,[11–15] SPECT data should therefore be acquired as early as possible. Usually data acquisition is performed at the time when brain activity reaches a plateau (e.g., at about 20 min). For quantitative rCBF measurements with ^{123}I-IMP and the microsphere model, reconstructed counts at a sufficiently early time are estimated by correcting the SPECT images obtained with the monitored total brain time activity curve.[4] This estimation is justifiable under the assumption that the activity distribution is uniform throughout the brain.

In this study, short time SPECT under various conditions proved to be useful in obtaining more correct and better rCBF mapping images. The shorter data acquisition and high reproducibility of the reconstructed counts are



"a": rCBFCt > rCBFCb ⟶ Ct(5)/Ct(40) > Cb(5)/Cb(40)

"b": rCBFCt = rCBFCb ⟶ Ct(5)/Ct(40) = Cb(5)/Cb(40)

"c": rCBFCt < rCBFCb ⟶ Ct(5)/Ct(40) < Cb(5)/Cb(40)

Fig. 6-a Relationship between $rCBF_{Cb}$ (ml//100 g/min) and $rCBF_{Ct}$ (ml//100 g/min). Lower perfusion areas and higher perfusion areas are expressed as "a" region and "c" region, respectively.

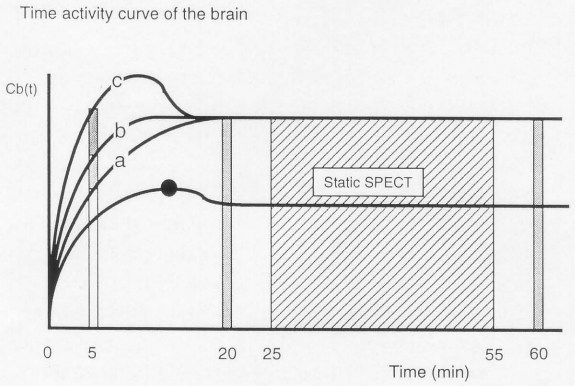


Fig. 6-b The schema of the time activity curves of ^{123}I-IMP derived from total brain ("b" region), lower perfusion areas ("a" region) and higher perfusion areas ("c" region). The early reference value is overestimated in low perfusion areas and underestimated in high perfusion areas. In pathologic lesion where Vd decreases (closed circle), the reference value is close to the one in the total brain concentration.

necessary. SPECT images acquired for one minute and reconstructed on 64 × 64 matrices (cut-off frequency 30 mm, order 4) were able to be used clinically. Correction of the static SPECT images by the regional tissue activity curve was shown to result in better rCBF ($rCBF_{Cb}$) mapping images.

Regional CBF_{Cb} correlated well with rCBF calculated from short time SPECT images at 5 min (rCBF) (Fig. 5). It was demonstrated, however, that rCBF calculated from static SPECT images with correction by the total brain time activity curve ($rCBF_{Ct}$), which was a popular method, was overestimated in the low flow areas, and underestimated in the high flow areas (Fig. 4). The relationship between $rCBF_{Ct}$ and $rCBF_{Cb}$ was similar to the relationship between $rCBF_{Ct}$ and rCBF (Fig. 6-a). Since $rCBF_{Ct}$ and $rCBF_{Cb}$ were calculated by using the same output and input functions, this discrepancy was considered to be due to the correction method used in estimating the early reference value.

The kinetics of ^{123}I-IMP is considered to be described by a two-compartment model.[9,10] Rate constants for extraction and back-diffusion are described as K_1 and k_2, respectively. In normal cerebral tissue, the distribution volume (Vd) is represented as K_1/k_2, which has a constant value.[5,16] In high flow areas, the time-activity curve rises rapidly, and the wash-out begins early. In low flow areas, the time activity curve rises slowly, and the brain activity reaches a plateau later (Fig. 6-b). The validity of this hypothesis was proved to be correct by simulation analysis.[5] The discrepancy between $rCBF_{Ct}$ and $rCBF_{Cb}$ is, therefore, considered to be caused by regional differences in the kinetic behavior of ^{123}I-IMP. At a sufficiently early time, activity in the high flow area ("c" region) and low flow area ("a" region) are higher and lower, respectively, than in the average flow area ("b" region). If the early reference value is calculated with correction by the total brain time-activity curve ("b" region), the value obtained may be underestimated in high flow areas and overestimated in low flow areas. The results of this study may be explained by this hypothesis.[17]

In a pathologic lesion, K_1 decreases and k_2 increases and, consequently, Vd decreases.[5,16] In such a lesion, rCBF decreases and wash-out. begins early, so that the cerebral concentration of ^{123}I-IMP becomes lower than that in normal tissue[5] (Fig. 6-b). The ratio of the concentration at 5 min to the concentration after 20 min in a pathologic lesion (closed circle) is close to the ratio in the total brain concentration ("b" region). This may be the reason why $rCBF_{Ct}$ in pathologic lesions, which were seen as low density lesions on X-CT, were close to rCBF in this study (closed circles in Figs. 4, 5, and 6).

In the present study, a more accurate method of measuring rCBF by means of ^{123}I-IMP SPECT with the microsphere models was proposed. The early reference value should be estimated by using the regional time activity curve to obtain more accurate rCBF values.

CONCLUSION

Quantitative cerebral blood flow measurements by means of ^{123}I-IMP SPECT with correction by the monitored total brain time-activity curve showed overestimation in the low flow area and underestimation in the high flow area. The error was considered to be due to the regional difference in the kinetic behavior of ^{123}I-IMP. It was concluded that more accurate rCBF values could be obtained with the regional time-activity curve.

APPENDIX

List of abbreviation used in the paper.

Ct(t): Total brain counts at t min
Cb(t): Reconstructed counts at t min, obtained by evaluating the counts for the region of interest on the SPECT images
Cb(25–55): Cerebral activity from 25 to 55 min derived from the SPECT images
$Cb(5)_{Ct}$: Reference value at 5 min corrected by total brain counts
$Cb(5)_{Cb}$: Reference value at 5 min corrected by reconstructed counts for the short time SPECT images
$rCBF_{Ct}$: rCBF calculated from static SPECT images corrected by total brain counts
$rCBF_{Cb}$: rCBF calculated from static SPECT images corrected by reconstructed counts for each ROI on the short time SPECT images

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