Annals of Nuclear Medicine Vol. 15, No. 1, 61–64, 2001

Validation of CBF measurement with non-invasive microsphere method (NIMS) compared with autoradiography method (ARG)

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The purpose of this study is to examine the correlation of measured regional cerebral blood flow (rCBF) by means of a new microsphere method (non-invasive microsphere method), to the autoradiography (ARG) method, which is an established quantification method for ^{123}I-IMP brain SPECT. The non-invasive microsphere (NIMS) method and ARG method were simultaneously applied to 30 patients, and quantified rCBF maps were calculated with each method. A significant correlation ($r = 0.70$: $p < 0.001$) was detected between mCBF values calculated with the NIMS and ARG methods. This new method seems to reliably quantify rCBF with brain SPECT.

Key words: ^{123}I-IMP (N-isopropyl-p-iodoamphetamine), regional cerebral blood flow, quantification, microsphere method, autoradiography method

INTRODUCTION

I-123 labeled N-isopropyl-p-iodoamphetamine (^{123}I-IMP) was developed by Winchell et al. and is used for estimating regional cerebral blood flow (rCBF).[1,2] It has a higher first pass extraction fraction and negligible wash out from cerebral tissue just after the injection.[3,4] ^{123}I-IMP is one of the most suitable commercially available SPECT tracers for quantification of rCBF with the microsphere method. Many quantification methods have been proposed for ^{123}I-IMP with arterial blood sampling.[3,5–8] Sugihara et al. and Miyazaki et al. have proposed a calculation method for cardiac output by first-pass transit of radiotracers.[9,10] This new method is appropriate for quantification of organ blood flow on the basis of the microsphere model. Yonekura et al. reported a quantification method for rCBF with this new method, which has been named the non-invasive microsphere (NIMS) method.[11] Nakano et al. examined the accuracy of NIMS with reference to continuous arterial blood sampling.[12] But, to the best of our knowledge, no other paper has focused on the comparison of the NIMS method with other quantification method. In this study, the accuracy of NIMS was examined by correlating it with the autoradiography (ARG) method.[6]

Received August 24, 2000, revision accepted November 16, 2000.

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MATERIALS AND METHODS

The NIMS and ARG methods were applied to 30 patients simultaneously (age; 47.3 ± 9.4, male/female; 18/12). Their clinical diagnoses/symptoms were 13 dizziness, 10 chronic fatigue syndrome, 7 headache. No patient has any disease affecting cardiac output and/or pulmonary flow.

Figure 1 illustrates the procedure of the NIMS and ARG methods. A dose of 222 MBq ^{123}I-IMP (Nihon Medi-Physics Co. Ltd., Japan) was injected rapidly into the right cubital vein. Dynamic scans including both lungs and heart area were performed from just after the bolus injection of ^{123}I-IMP. We use MAXXUS (General Electric Co. Ltd., USA) equipped with low-energy high-resolution type collimator. Scan conditions were as follows: scan time: 3 minutes, frames: 2 frames/second, view: anterior, matrix: 128 × 128.

Hands selected regions of interest (ROIs) including whole lung and pulmonary artery and time-activity curves of both ROIs were obtained. The total pulmonary count at peak time: L(peak) was found, and the total pulmonary count 5 minutes after the injection: L(5) was calculated by exponential approximation with the pulmonary count data from L(2) to L(3). The lung washout rate 5 minutes

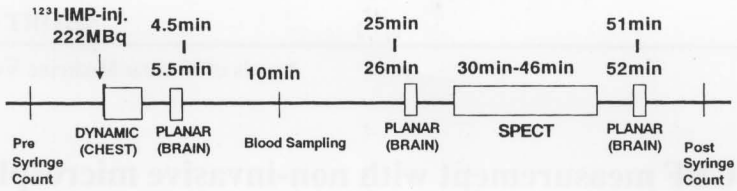

Fig. 1 The schema of the NIMS and ARG method.

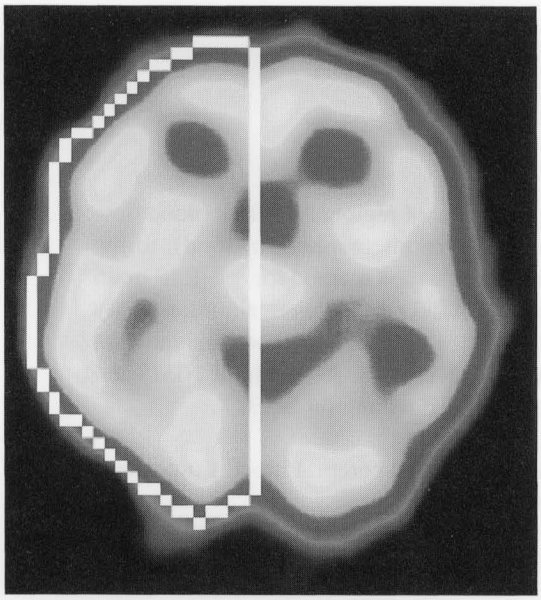

Fig. 2 ROI for mCBF.

after injection was calculated as {L(peak) − L(5)} / L(peak). The time-activity curve of the pulmonary artery was fitted to an exponential curve, and the area of this time-activity curve during the first pass was calculated (R). Cardiac output (CO) was calculated from R and the total injected dose of ^{123}I-IMP after dead time correction, and the results of Doppler echocardiography were correlated according to the method of Sugihara et al.[9] Correlated cardiac output (CO′) was calculated as follows:

$$CO' = 28.8 \times CO^{0.634}$$

From 4.5, 25 (before SPECT) and 51 (after SPECT) minutes after the injection, a brain planar image was taken with these conditions: scan time: 1 minute, view: anterior, matrix: 128 × 128. A ROI including the whole brain was drawn on a brain planar image by hand, and the total brain counts at 5 minutes after the injection: B(5), just before SPECT: B(before), and just after SPECT: B(after) were obtained.

Brain SPECT was performed from 30 minutes after injection of ^{123}I-IMP. The scan conditions were: scan time: 16 minutes, step: 30 seconds/step total 32 steps, prefilter: Butterworth (cut off; 0.45 cycle/cm, order; 10), backprojection-filter: ramp, matrix: 64 × 64, collimator: low-energy high-resolution type, gamma camera: MAXXUS. Regional CBF was calculated as follows[11,13]:

$$rCBF = rSPC \times CBF\ factor$$
$$CBF\ factor\ (ml/100\ g/min) = K \times [B(5)/\{B(before) + B(after)\}/2] \times CO' \times D(1.04\ g/ml) \times 100/[Q \times \{1 - L(5)/L(peak)\}]$$

rSPC: regional SPECT count
K: Correlation factor of SPECT count to planar count that was measured in the phantom study with ^{123}I-IMP
Q: Total injected dose of ^{123}I-IMP
D: Density of cerebral parenchyma

The factor K was the ratios of SPECT to total planar count and defined as the ratio of phantom SPECT count and difference between syringe counts before and after injection of ^{123}I-IMP into phantom. We used an acryl syrindlical phantom (16 centimeters in diameter) which was filled with 37 MBq of ^{123}I-IMP solution. The scan conditions of SPECT and planar image in the phantom study were identical to those of clinical SPECT and planar image. A deadtime correction was also performed on the basis of the phantom study. The total injected dose of ^{123}I-IMP (Q) was regarded as the difference between the pre-injection and post-injection syringe counts.

Arterial blood sampling was done 10 minutes after the injection from the right cubital artery. The total blood count was measured with a well type scintillation counter (ARC 256, Aloka Co. Ltd., Japan). The standard input function of the ARG method proposed by Iida et al.[6] was correlated with this count. Calculation of rCBF and construction of rCBF maps by the two methods were performed automatically with software supplied by the manufacturer (General Electric Co. Ltd., USA).

The mean CBF (mCBF) was the mean rCBF of the right cerebral hemisphere at the level of the basal ganglia (Fig. 2). The significance of the correlation between mCBF values with the NIMS and ARG methods was examined by linear regression test.

RESULTS

The distribution of CO′ is shown in Figure 3. Figure 4 shows the correlation between the NIMS and ARG methods. A significant correlation ($r = 0.70$: $p < 0.001$) was

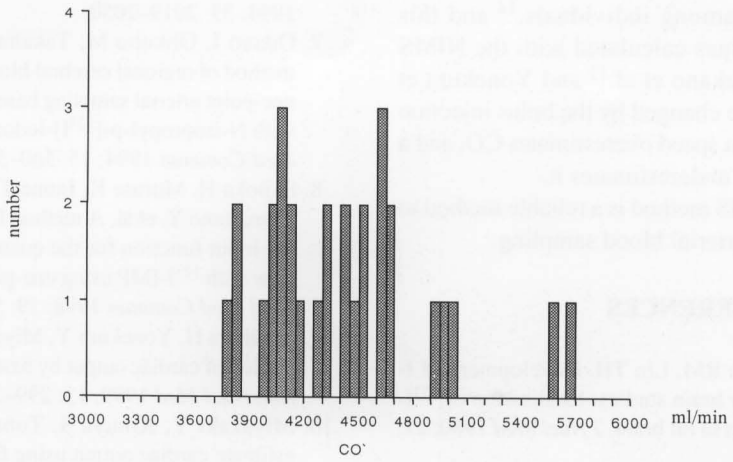

Fig. 3 Distribution of CO'. Mean and standard deviation of correlated cardiac output were 4426 ml/min and 465 ml/min.

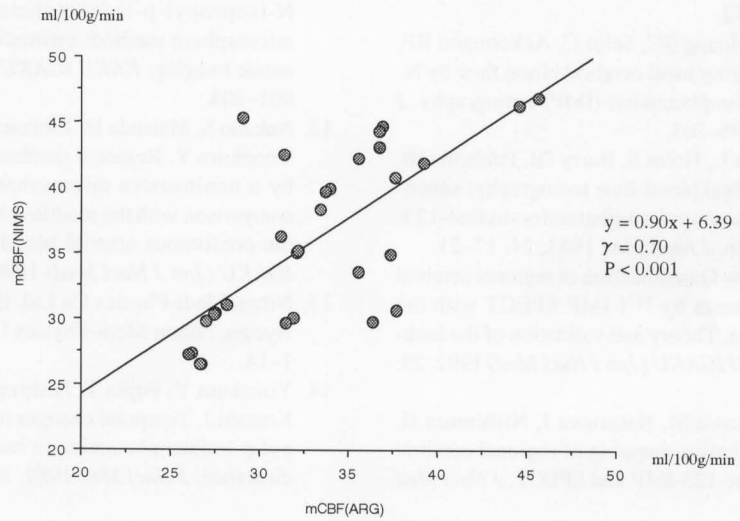

Fig. 4 Comparison of mCBF values using NIMS and ARG method. Each mark corresponds to mCBF values of each subject. A significant correlation was confirmed between the two methods ($r = 0.70$: $p < 0.001$).

detected between mCBF values by the NIMS and ARG methods.

DISCUSSION

^{123}I-IMP is frequently used for estimating rCBF values. Various methods are proposed to quantify rCBF with ^{123}I-IMP,[3,5–8] most of which require arterial blood sampling, thereby limiting their clinical applicability. Among them, the NIMS method does not require arterial blood sampling. The NIMS method is based on the microsphere theory. A good correlation of the NIMS method to the microsphere method with continuous arterial blood sampling[12] ensured the accuracy of the former. The ARG method requires only a single arterial blood sampling and it can correlate back diffusion of ^{123}I-IMP. Iida et al. reported a significant correlation ($r = 0.85$) between rCBF values calculated with the ARG method and those calculated with PET by $H_2{}^{15}O$.[6] In this study we compared the rCBF values obtained with the NIMS method with those obtained with the ARG method. A significant correlation ($r = 0.70$: $p < 0.001$) between the two methods again confirmed the accuracy of the NIMS method.

Future improvements in the NIMS method will include correction to the lipophilic fraction of ^{123}I-IMP, delayed washout of ^{123}I-IMP from the lungs, and uniformity of the bolus injection speed. ^{123}I-IMP is metabolized in blood, and estimation and correlation of the lipophilic fraction of ^{123}I-IMP are necessary for the NIMS method as with other quantification methods. The washout speed of ^{123}I-IMP

from the lungs differs among individuals,[14] and this influences the rCBF values calculated with the NIMS method. As noted by Nakano et al.[12] and Yonekura et al.,[11] the CO value can be changed by the bolus injection speed. A too fast injection speed overestimates CO, and a too slow injection speed underestimates it.

In conclusion, the NIMS method is a reliable method to quantify rCBF without arterial blood sampling.

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