Verification of a Newly Developed Noninvasive Method for Estimating Cerebral Blood Flow Using ^{123}I-IMP Acquisition Data from the Lungs and Brain

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ABSTRACT

Objective: Previously, we devised a method for estimating ^{123}I-IMP activity at 10 min after intravenous injection of ^{123}I-IMP (Ca10) without any blood sampling using ^{123}I-IMP autoradiography (ARG) acquisition data, and verified its usefulness for quantification of the regional cerebral blood flow (rCBF). In this study, we attempted to develop a more simplified method for estimation of Ca10 and to evaluate its usefulness for quantification of rCBF in a number of patients with different cerebrovascular diseases.

Methods: Consecutive 134 patients were examined for ^{123}I-IMP ARG study. Dynamic images of the lungs for 5 min and brain SPECT images for 30 min (6×5 min) and Ca 10 values were acquired from the first 35 patients. Using the data of the 35 patients, the regression equation for estimating Ca10 was calculated by the multiple regression analysis. The regression equation was applied to the other 99 patients who comprised 29 patients with Parkinson's disease, 32 with common or internal carotid artery occlusion or stenosis, 14 with moyamoya disease, 12 with cerebral infarction, and 12 with other diseases. The mean of rCBFs in various regions of the brain (meanCBF) calculated using the estimated Ca10 was compared with that calculated using directly measured Ca10 in the 99 patients.

Results: The regression equation obtained was as follows: Estimated Ca10 = 1070.1 + 2.17 $\times 10^{-3}$a − 8.08 · b − 2.23 × c + 2.47 $\times 10^{-3}$d, where a: the area under the time-activity curve of

the lungs (UCL), b: body weight, c: sum of UCL and the counts of brain projection data from 10 to 15 min after injection (CB1), d: those from 35 to 45 min (CB6), respectively. The estimated Ca10 closely correlated with the directly measured Ca10 (r=0.77). The meanCBF values calculated using the estimated Ca10 closely correlated with those calculated using the directly measured Ca10 in all the patient groups (r=0.795, 0.784, 0.624, 0.771, 0.854 and 0.785 in patients with Parkinson's disease, common or internal carotid artery occlusion or stenosis, moyamoya disease, cerebral infarction, and the other diseases, and the total 99 patients, respectively).

Conclusion: This study verified that the newly developed noninvasive method, which is more simplified than the previous method, can estimate reliably the Ca10 values which are available for quantification of rCBF in different patient groups.

1. INTRODUCTION

It is identified that brain physiologic activity depends on regional cerebral flow (rCBF). Since deficits in rCBF usually give rise to pathological changes of the brain, measurements of rCBF have so far continued to be an important clinical assignment.

In the past, a number of studies were performed for rCBF quantification using ^{123}I-iodoamphetamine (IMP) and SPECT based on the microsphere model or the one-tissue compartment model (1-7). The methods reported in these studies require continuous or one-point arterial blood sampling by arterial puncture which is invasive for the patients to be examined by the methods. Among these studies, the method developed by Iida et al. (^{123}I-IMP ARG method) (3, 4) has been frequently used as a relatively simple and reliable method for rCBF quantification. In the method, however, one-point arterial blood sampling is still needed for determination of arterial input function for each subject, although continuous arterial blood sampling and measurement of the lipophilic fraction in the blood samples were avoided.

To avoid arterial blood sampling, studies were made for rCBF quantification using ^{123}I-IMP and SPECT with venous blood sampling (8, 9) or without any blood sampling (10-12). Two of the methods without any blood sampling were based on the microsphere model, and

calculated the input function by using dynamic lung images and estimated cardiac output (10, 11). In another one (12), the integral of arterial input function was estimated using dynamic lung images by the single regression analysis instead of continuous arterial blood sampling.

Previously, we devised a method without any blood sampling for estimating ^{123}I-IMP arterial blood activity at 10 min after intravenous injection of ^{123}I-IMP (Ca10), in which the multiple regression analysis was conducted to estimate Ca10 using 5 parameters from the lung washout counts, time series of brain static counts, and brain SPECT average counts as the explanatory variables and the Ca10 directly measured with the actual arterial blood sample as the objective variable, and the regression equation to estimate Ca10 was calculated (13). The results of the previous study indicated that the estimated Ca10 values closely correlated with the directly measured Ca10 values, the mean of rCBFs in various regions of the brain (mean CBF) calculated by ^{123}I-IMP ARG method (4, 5) using the estimated Ca10 also closely correlated with those calculated using the directly measured Ca10, and the mean CBF values calculated by the ^{123}I-IMP ARG method using either the directly measured or the estimated Ca10 significantly correlated with those measured by ^{15}O-H_2O positron emission tomography (PET) ARG method (14, 15). Then we developed an improved noninvasive method for estimating rCBF, in which an integral of the arterial blood

counts during the time after injection of ^{123}I-IMP (∫Ca) was calculated in place of Ca10, and the mean CBF values obtained approximated more accurately to the values measured by ^{15}O-H_2O PET ARG method than those obtained by the previous method (16). Nevertheless, our methods (13, 16) seemed to be still rather complicated and the development of a more simplified technique for rCBF quantification was expected. This is a direct motive for conducting the present study.

2. MATERIALS AND METHODS

Patients

Consecutive 134 patients, who underwent rCBF quantification by ^{123}I-IMP ARG method in our university hospital between April 2012 and February 2014, were enrolled in this retrospective study. The acquisition data from the first 35 patients were utilized in calculating the regression equation for estimating Ca10. The acquisition data from the other 99 patients were examined for the applicability of the regression equation. The profiles of the first 35 patients and the other 99 patients are shown in Tables 1 and 2, respectively. All these study patients had no respiratory disorders. All procedures followed the clinical guidelines of Nagoya University Hospital and were approved by the institutional review board. A complete description of the study was given to all participating patients and a consent form was signed by the patients.

^{123}I-IMP data acquisitions with gamma camera

Outlines of the procedures of ^{123}I-IMP data acquisition by gamma camera are shown in Figure 1. Gamma camera and SPECT-CT used were the two-detector type Symbia T equipped with a low-medium-energy general purpose (LMEGP) collimator (Siemens Healthcare, Erlangen, Germany). One hundred sixty-seven MBq of ^{123}I-IMP (Nihon Medi-Phsics Co., Ltd.) was infused into the antecubital vein at a constant rate for 1 min. Each patient underwent a dynamic planar scan of the lungs for 5 min immediately after intravenous injection of ^{123}I-IMP (1 second / frame 300 frame, matrix size: 128) (Figure 2). Then one-point arterial blood sampling was made 10 min after injection of ^{123}I-IMP, followed by brain SPECT data acquisitions. SPECT data acquisitions were performed around 360 degrees with matrix size 128×128 and in continuance rotation with an angular step 4° every 5 min, and the data acquisitions were made 6 times. After that, CT image was taken to acquire data for attenuation correction. The projection data obtained by SPECT were reconstructed by filtered back projection with a Butterworth filter (cutoff frequency: 0.65 cycles/cm). Scatter correction was made by the triple energy window method; 24% at the main scatter window around 159keV and 8% at both the upper and lower scatter windows. To determine the radioactivity in the arterial blood taken at 10 min after ^{123}I-IMP

injection (Ca10), the arterial blood samples were dispensed in triplicate as 0.5ml aliquots into tubes. After subtracting the background count, the tubes measured for 3 min using an Auto-Well Gamma System (AccuFLEXα700, Aloka). The rCBF values were calculated using Ca10 and ^{123}I-IMP acquisition data according to the ^{123}I-IMP ARG method descried by Iida et al. (4, 5).

Data Analysis

A region of interest (ROI) covering both lung fields was set to determine an accumulation and a clearance of ^{123}I-IMP from the lungs. Time course of the radioactivity of the lungs after intravenous injection of ^{123}I-IMP is shown in Figure 2. The radioactivity of the lungs reached the peak at 30 to 40 seconds after intravenous injection of ^{123}I-IMP, and declined thereafter until about 3 min, and maintained a nearly constant level until 5 min after injection. The area under the time-activity curve of the lungs for 5 min after injection (UCL), which is equivalent to the integral of the radioactivity in the lungs, was calculated (counts per second/gram (cps/g)).

The brain SPECT images after reconstruction and attenuation and scatter corrections, which were taken for each 5 min, namely, 10-15, 15-20, 20-25, and 35-40 min after injection of ^{123}I-IMP, were examined for measuring the accumulation of the radioactivity; the values were designated as CB1, 2, 3, 4, 5, and 6,

respectively.

All the reconstructed images were applied to the three-dimensional automatic ROI analysis software 3D-SRT (Fuji Film RI Pharma Co., Ltd.) (17,18). The SPECT images were anatomically standardized using SPM99, followed by quantification of tracer accumulation in 12 segments (anterior, precentral, central, parietal, angular, temporal, occipital, pericallosal, lenticular nucleus, thalamus, hippocampus, and cerebellum) in both semispheres of the brain. The mean of rCBF values (mean CBF) in 12 segments of the brain was calculated in each patient. The mean CBF values were used for comparison between rCBF calculated using the estimated Ca10 and that calculated using the directly measured Ca10.

Statistical Methods

All data were statistically analyzed using the STATCEL 2 (OMS Publishing Inc.). In multiple regression analysis, the regression equation was calculated using the least squares method. The data used as the explanatory variables and the objective variable were confirmed to follow a normal distribution using x^2 test. Pearson correlation coefficient test was applied to the level of significance of the correlation coefficient. The significance of the difference between the two correlation coefficients was determined by the test of equivalence of the correlation coefficient using STATISTICA version 0.3 (Stat Soft, Inc.). Statistical significance was established for $p< 0.01$.

3. RESULTS

Multiple regression analysis for the estimation of Ca10

Outlines of the procedures of ^{123}I-IMP data acquisition with gamma camera from the lungs and brain for a study patient are shown in Figures 1 and 2. The regression equation for the estimation of Ca10 was derived by the multiple regression analysis using the directly measured Ca10 as the objective variable and the area under the time-activity curve of the lungs for 5 min after injection of ^{123}I-IMP (UCL), the counts of the brain accumulated from 10 to 15 min after injection (CB1), those from 35 to 40 min after injection (CB6), and body weight (b) as the explanatory variables. As a result, the following regression equation was obtained:

Estimated Ca10 = 1070.1 + 2.17 × 10^{-3}·UCL −8.08 · b − 2.23 ×10^{-3}· (UCL+CB1) +2.47 ×10^{-3}·CB6 (cps/g).

Comparison between the estimated Ca10 and directly measured with the actual arterial blood sample (the directly measured Ca10)

Figure 3 shows the correlation between the estimated Ca10 and the Ca10 directly measured with the actual arterial blood sample (cps/g) in the total 99 patients. There is a close correlation between the estimated Ca10 and the directly measured Ca10 in the total 99 patients ($r=0.77$, $p<0.01$).

Comparison between the mean CBF values calculated by ^{123}I-IMP ARG

method using the estimated Ca10 and those calculated using the directly measured Ca10

Figure 4A-F show the correlation between the mean CBF values (ml/100g/min) calculated by ^{123}I-IMP ARG method using the estimated Ca10 and those calculated using the directly measured Ca10 in patients with Parkinson's disease (A), common or internal carotid artery occlusion or stenosis (B), moyamoya disease (C), cerebral infarction (D), the other diseases (E), and the total 99 patients (F). There is a close correlation between the mean CBF values calculated using the estimated Ca10 and those calculated using the directly measured Ca10 in all the patient groups (r=0.795 in A, 0.784 in B, 0.624 in C, 0.771 in D, 0.854 in E, and 0.785 in F). There are no statistically significant differences among all these correlation coefficients for various patient groups.

Exemplary rCBF images of the brains of patients with various diseases obtained by ^{123}I-IMP SPECT

Figure 5 shows rCBF images of brain obtained by ^{123}I-IMP SPECT and the SPECT images treated with 3D-SRT in patients with Parkinson's disease (A), internal carotid artery stenosis (B), moyamoya disease (C), and cerebral infarction (D).

4. DISCUSSION

The first radionuclide used for quantification of rCBF was ^{133}Xe, which was principally inhaled by the patient, and

the measurements were made with scintillation detectors on the scalp (19). Then, there was the rapid development of scanning devices and SPECT became the ordinary method for rCBF quantification. The radiopharmaceuticals which were found to be appropriate to rCBF quantification using SPECT were ^{123}I-IMP (20), the 99mTc-labeled compounds hexamethyl propyleneamine oxime (HMPAO) (21), and ethyl cysteinate dimer (ECD) (22). The method for rCBF quantification using positron emission tomography (PET) ARG with O-15 H_2O was developed (23, 24). Among the methods so far developed for rCBF quantification, the methods using ^{123}I-IMP and SPECT were mostly investigated and also widely used (1-7). Since they are still invasive for the patients, we have begun to search for the noninvasive technique for rCBF quantification without any blood sampling that can be used as an easy clinical examination.

In the present study, the correlation coefficients between the mean CBF values calculated using the estimated Ca10 and that calculated using the directly measured Ca10 in the total 99 patients with various cerebrovascular diseases was very similar to that obtained by the first study of this series (r=0.785 vs. 0.818) (13).

In the first and the succeeding studies of this series, no attenuation corrections were carried out for the ^{123}I-IMP acquisition data from the lungs, whereas attenuation and scatter corrections were made in the SPECT

images (13, 16). There might be possibilities that attenuation factors in the planar lung images vary dependently upon patients. In place of the assumed attenuation factors, we tried to use the body weight as one of the explanatory variables in the multiple regression analysis for acquiring the estimated Ca10. As a result, we could reduce the parameters related to the ^{123}I-IMP acquisition data which were used in the calculation of the regression equation for estimating Ca10, to the following three; UCL, CB1, and CB6. Still now, further studies are in progress to develop a more accurate and simplified noninvasive method for rCBF quantification.

5. CONCLUSION

This study verified that the newly developed noninvasive method for estimating Ca10, which is more simplified than our previous method, can be reliably applied for rCBF quantification in the total 99 patients with different cerebrovascular diseases.

Compliance with ethical standards

Conflicts of interest: The authors declare that they have no conflict of interest.

Ethical approval: This study was approved by the Institutional Review Board (13-318). All procedures performed in studies involving human participants were performed in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For retrospective studies such as ours formal consent is not required.

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TABLES AND FIGURES

TABLE 1. Profiles of the patients examined for calculating the regression equation

Patients	Number	Age range (mean ± SD) years	Male/female
Parkinson's disease	23	55-80 (69.13 ± 7.31)	10/13
Common or internal carotid artery occlusion or stenosis	5	21-77 (58.80 ± 21.74)	4/1
Moyamoya disease	2	17-45 (31 ± 19.80)	0/3
Cerebral infarction	3	42 (42 ± 0.00)	3/0
Common carotid artery dissection	1	65	1/0
Middle cerebral artery stenosis	1	77	1/0
Total	35	17-80 (62.76 ± 15.32)	19/16

TABLE 2. Profiles of the patients examined for evaluating clinical usefulness of the method shown in this study

Patients	number	Age range (mean ± SD) years	Male/female
Parkinson's disease	29	49-78 (68.55 ± 6.74)	9/20
Common or internal carotid artery occlusion or stenosis	32	49-81 (68.75 ± 9.11)	29/3
Moyamoya disease	14	25-66 (40.29 ± 12.44)	3/11
Cerebral infarction	12	36-71 (51.92 ± 12.24)	5/7
Others*	12	38-79 (55.08 ± 13.58)	3/9
Total	99	25-81 (60.97 ± 14.40)	49/50

*Others comprised 12 patients with middle cerebral artery occlusion or stenosis (3 patients), with aortitis syndromes (2 patients), with motor neuron disease (1 patient), with essential tremor (1 patient), with spinocerebellar degeneration (1 patient), with dementia (1 patient), with red nucleus tremor (1 patient), with transient ischemic attack (TIA, 1 patient) and with homonymous hemianopsia (1 patient).

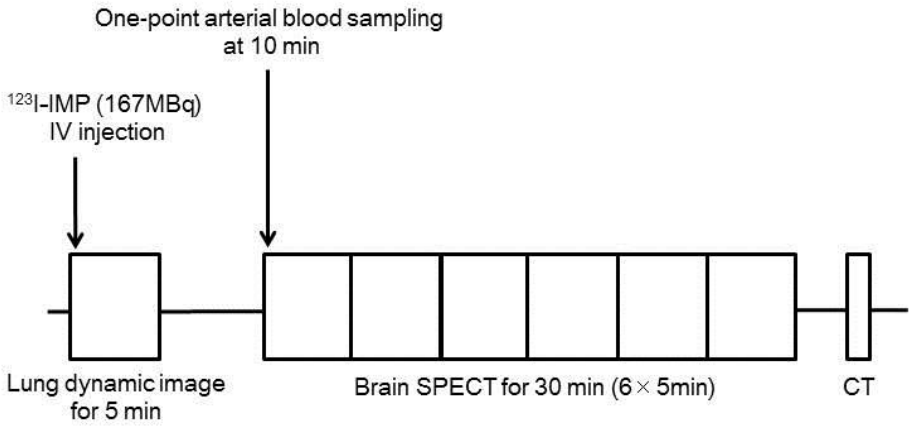

FIGURE 1. Outlines of the procedures of ^{123}I-IMP data acquisition with gamma camera by the method shown in this study.

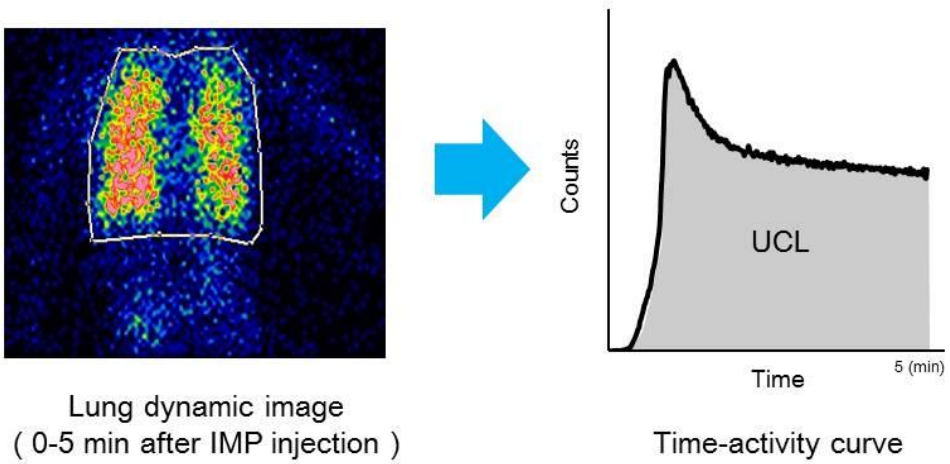

FIGURE 2. The area under the time-activity curve of the lungs (UCL)

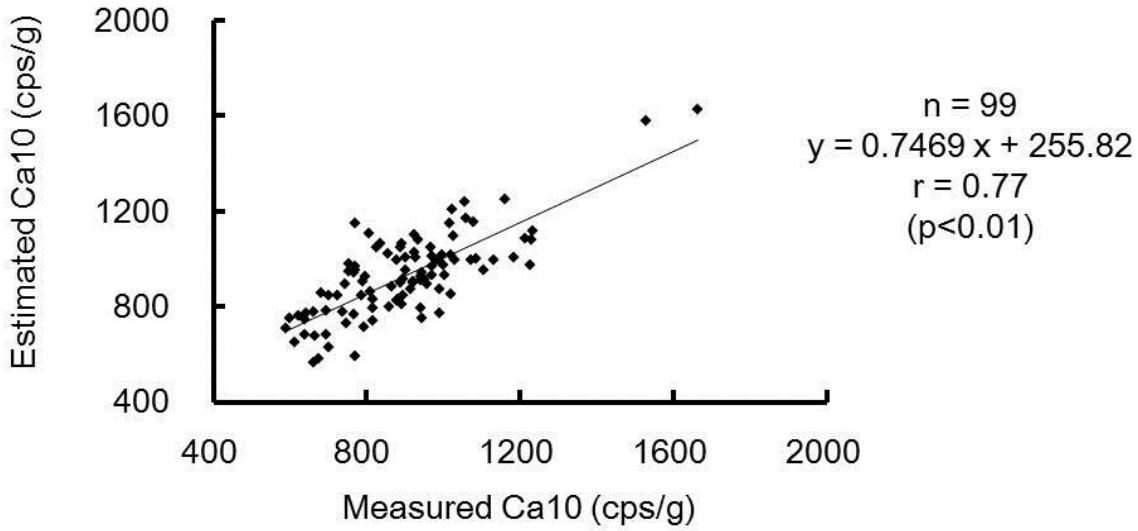

FIGURE 3. Comparison between the estimated Ca10 and the directly measured Ca10 in the total 99 patients.

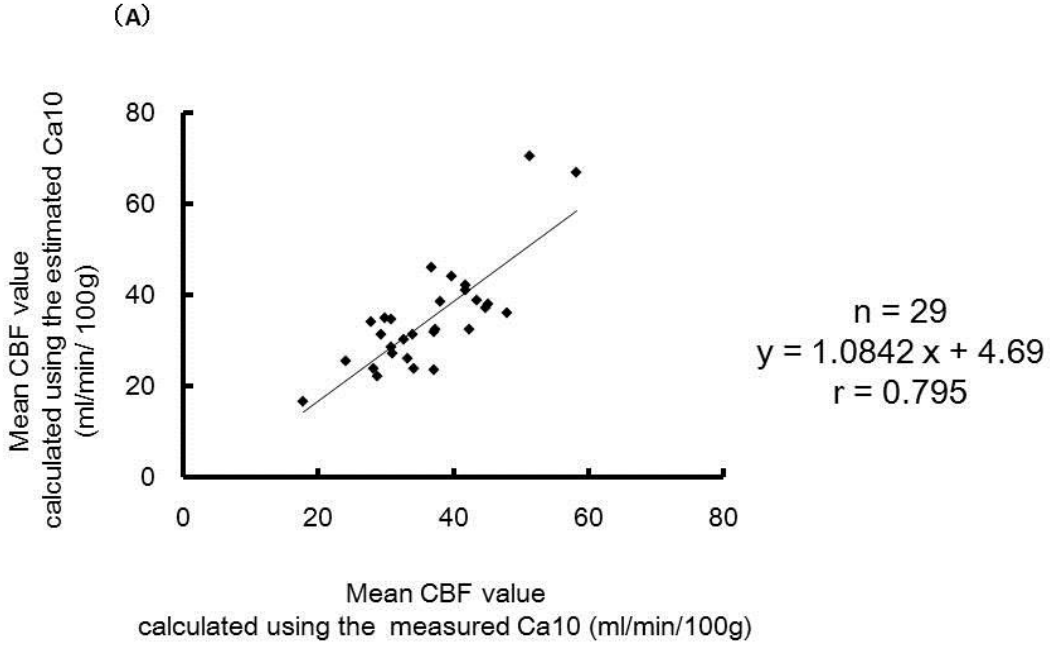

FIGURE 4-A. Comparison between the mean CBF values calculated using the estimated Ca10 and those calculated using the directly measured Ca10 in patients with Parkinson's disease.

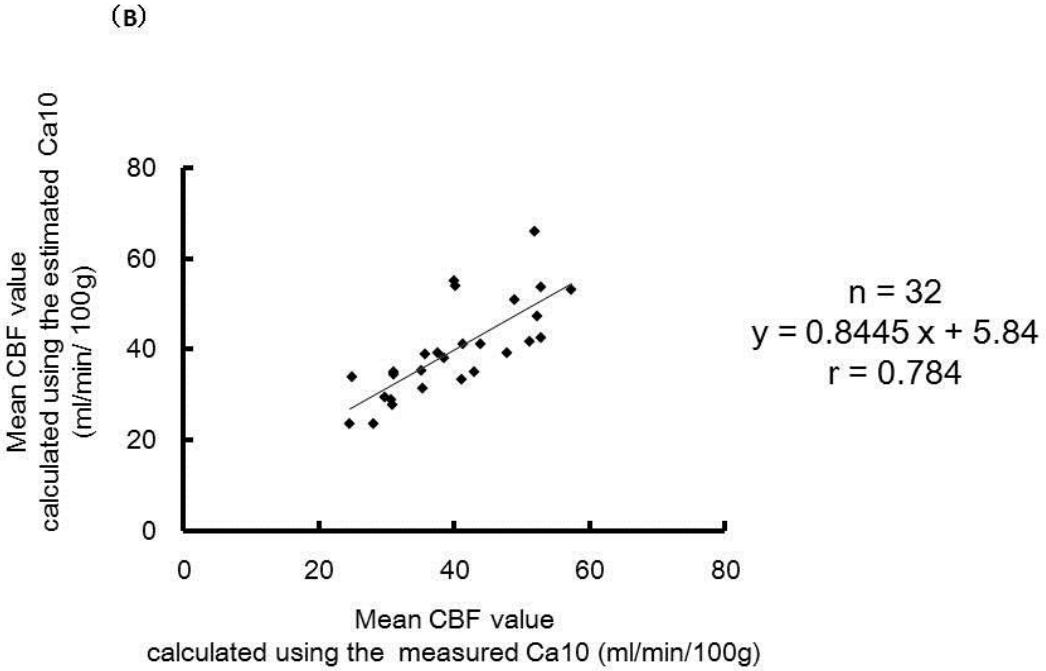

FIGURE 4-B. Comparison between the mean CBF values calculated using the estimated Ca10 and those calculated using the directly measured Ca10 in patients with common or internal carotid artery occlusion or stenosis.

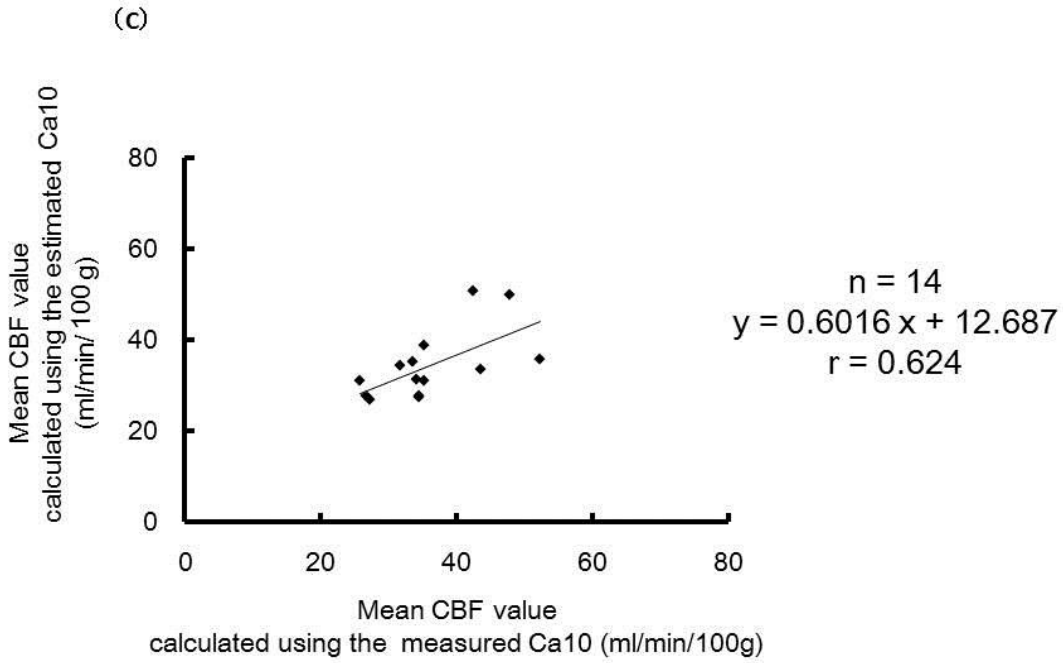

FIGURE 4-C. Comparison between the mean CBF values calculated using the estimated Ca10 and those calculated using the directly measured Ca10 in patients with moyamoya disease.

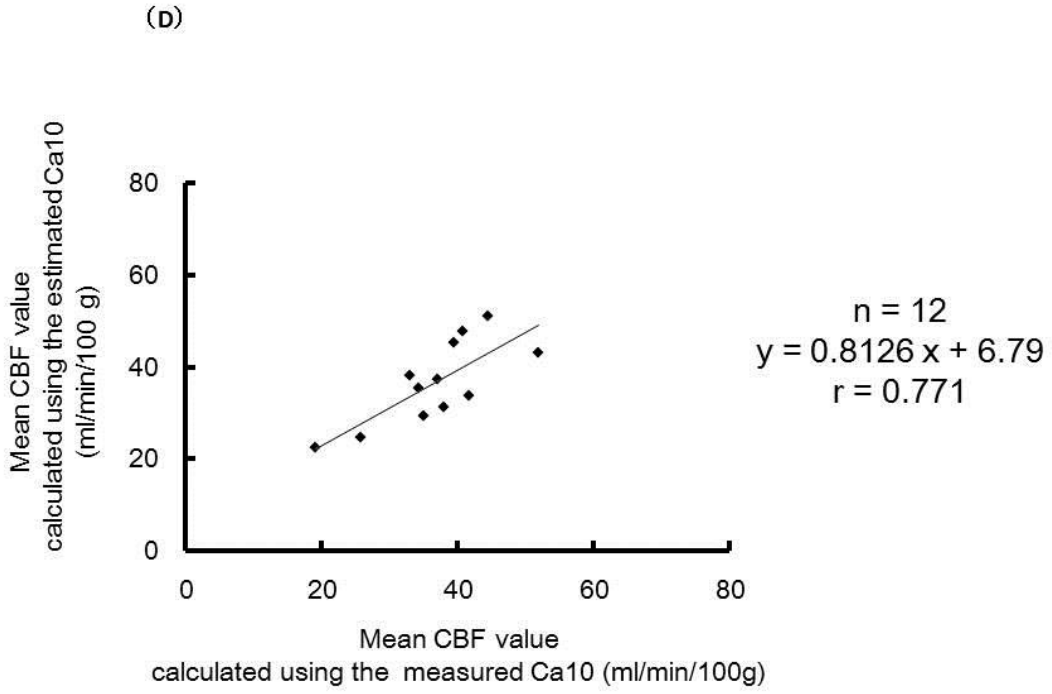

FIGURE 4-D. Comparison between the mean CBF values calculated using the estimated Ca10 and those calculated using the directly measured Ca10 in patients with cerebral infarction

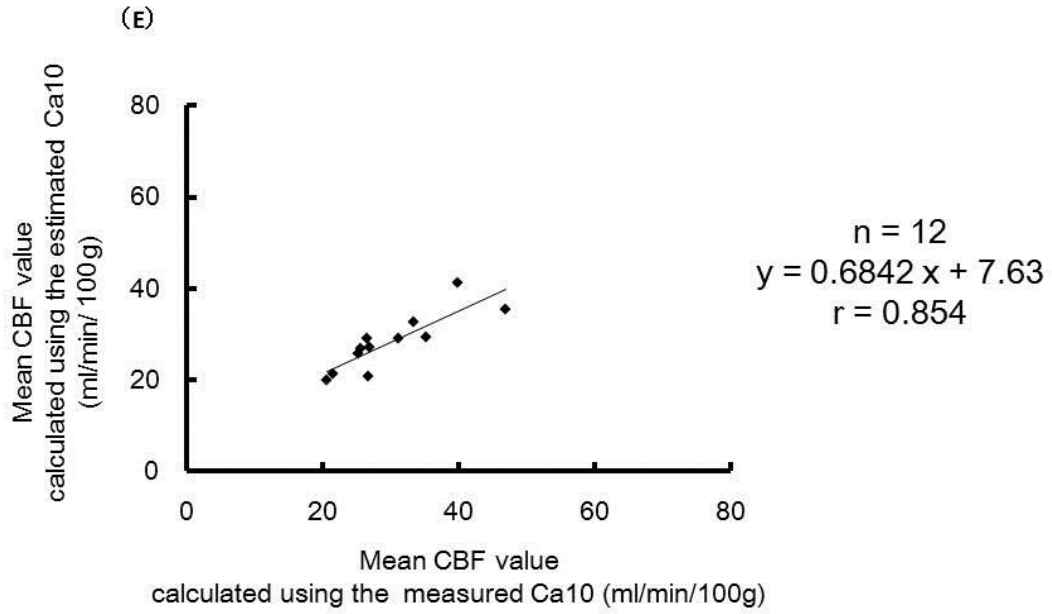

FIGURE 4-E. Comparison between the mean CBF values calculated using the estimated Ca10 and those calculated using the directly measured Ca10 in patients with the other diseases.

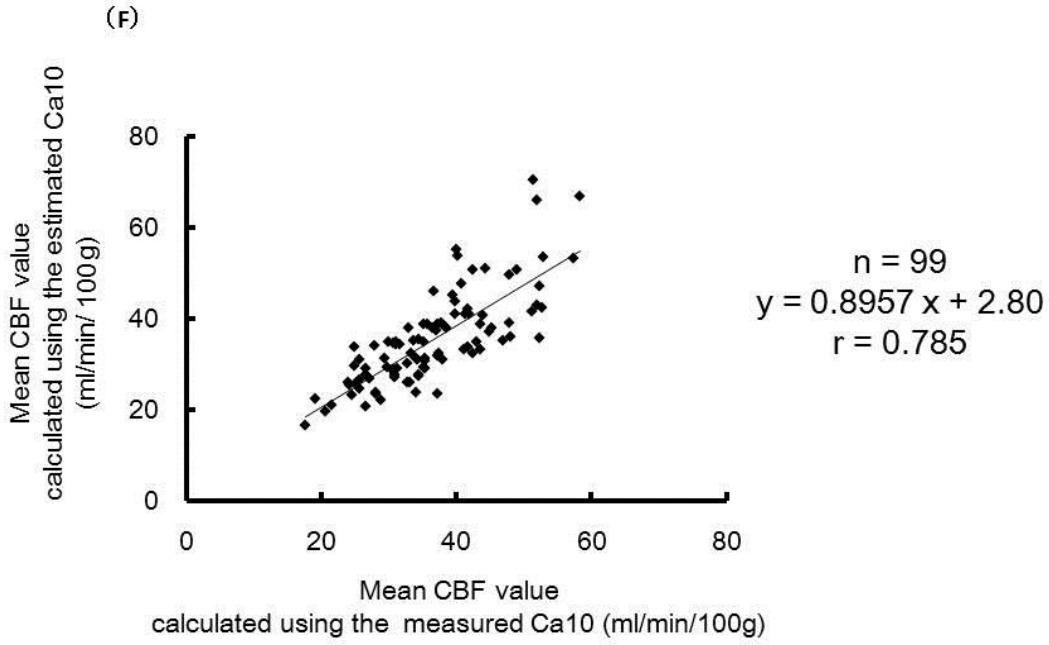

FIGURE 4-F. Comparison between the mean CBF values calculated using the estimated Ca10 and those calculated using the directly measured Ca10 in the total 99 patients.

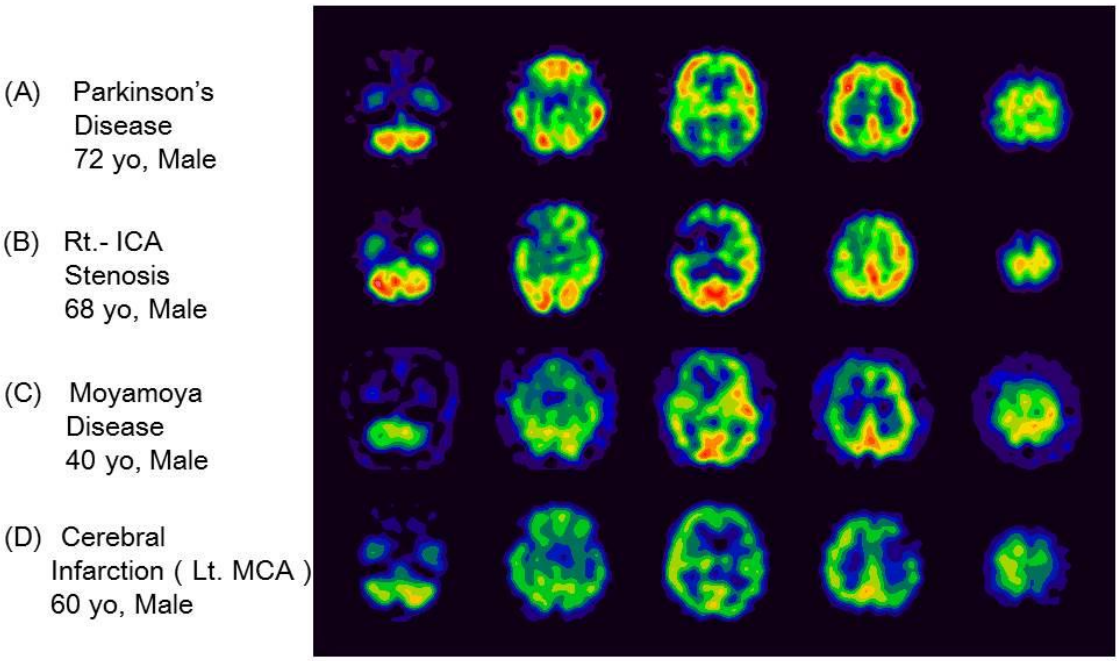

Figure 5. Exemplary rCBF images by ^{123}I-IMP SPECT in patients with Parkinson's disease (A), right internal carotid artery (ICA) stenosis (B), moyamoya disease (C), and cerebral infarction (left middle cerebral artery (MCA)) (D).

