Estimation of ^{123}I-IMP arterial blood activity from dynamic planar imaging of the chest using a graph-plot method for the quantification of regional cerebral blood flow

Seiji Tomiguchi*, Kuniyuki Tashiro**, Shinya Shiraishi**, Morikatsu Yoshida**, Koichi Kawanaka**, Yoshitake Takahashi***, Tsutomu Soma***, Yasuyuki Yamashita**

*Department of diagnostic radiology, School of health sciences, Kumamoto University, Kumamoto, Japan

**Department of Diagnostic Imaging, Faculty of Medical and Pharmaceutical Sciences, Kumamoto University, Kumamoto, Japan

***Clinical Application Technology Department, FUJIFILM RI Pharma Co., Ltd., Tokyo, Japan

Corresponding author,
Seiji Tomogichi MD
Diagnostic radiology, School of Health Sciences, Kumamoto University
4-24-1, Honjo, Kumamoto, 862-0976, Japan
TEL& FAX: +81-96-373-5504
E-mail: seiji@kumamoto-u.ac.jp

Abstract

Purpose: I-123 labeled N-isopropyl-p-iodoamphetamine(^{123}I-IMP) is used for measurement of regional cerebral blood flow(rCBF). A continuous or single arterial blood sampling(ABS) is necessary to estimate an integral of arterial input function(AIF) for the measurement of rCBF by using a microsphere model analysis. Therefore, the method to measure rCBF without any blood sampling is desired. The aim of this study was to establish the method to estimate the AIF from the time-activity curve of the lungs after the injection of ^{123}I-IMP using a regression analysis for the measurement of rCBF without any blood sampling.

Materials and methods: Thirty-seven prospective studies in 10 consecutive patients were enrolled. A chest planar dynamic imaging for 3 minutes and continuous ABS for 5 minutes after a bolus injection of 167MBq ^{123}I-IMP were performed in all studies. Data from the chest imaging were analyzed in comparison with ABS data(AIF(5)) in the first 10 studies, and an equation for estimation yielding accurate AIF(5) from the total counts cleared from the lungs during 5 minutes after injection of ^{123}I-IMP(TCL(5)) was derived. The validity of the proposed method was evaluated in the subsequent 27 studies.

Results: A good correlation was obtained between the AIF and TCL by regression analysis in the first 10 studies($r=0.94$, $p<0.001$). An equation for the

estimation of AIF by the regression analysis in the first 10 studies was defined as follows, estimated AIF=2146.7336 +4.1735xTCL(5). In the subsequent 27 studies, a good linear correlation was obtained between measured AIF(5) and estimated AIF(5) by using the equation($r=0.79$, $p<0.001$).

Conclusion: AIF(5) can be accurately estimated from the TCL(5). Therefore, estimated AIF(5) can be used for the measurement of rCBF instead of ABS data.
Key words: CBF measurement, arterial input function, ^{123}I-IMP, Pulmonary dynamic imaging

Introduction

I-123 labeled N-isopropyl-p-iodoamphetamine(^{123}I-IMP) is used for measurement of regional cerebral blood flow(rCBF)1). It has a higher first pass extraction fraction and negligible back diffusion from cerebral tissue just after the injection1-2). These favorable chemical properties of ^{123}I-IMP show a linear relationship between ^{123}I-IMP accumulation and blood flow in regional cerebral tissues. ^{123}I-IMP is one of the most suitable radiopharmaceuticals for quantification of rCBF with the microsphere model1)3-4) or two-compartment model5-8) analysis. Several simplified methods proved to provide reliable rCBF values with performing a ^{123}I-IMP brain SPECT and arterial blood sampling9-10).

A quantification method of rCBF using ^{123}I-IMP and SPECT without any blood sampling(non-invasive microsphere method:NIMS) is also proposed11-13). This method uses a planar dynamic imaging of the chest for 3 minutes after an bolus injection of ^{123}I-IMP to estimate cardiac output(CO) and total amount of ^{123}I-IMP delivered to the whole body in T minutes[TC(T)]. If T is acceptably small, rCBF can be determined based on the microsphere model analysis with ^{123}I-IMP as Cb(T)/(TC(T)/CO), where Cb(T) is cerebral radioactivity at T minutes and TC(T)/CO is integral of arterial input function. However, the process to estimate for the arterial input function is very complicated in this method.

^{123}I-IMP accumulates in the lungs after an intravenous injection and is gradually released from the lung into the systemic circulation12). Assuming that peak counts of the lung represent the injected dose and re-circulation of the ^{123}I-IMP is negligible in T minutes12-13), the integral of arterial input function during T minutes(AIF(T)) reflects the counts in the lungs released between peak time and T minutes(total clearance counts from the lung at T minutes: TCL(T)). The first-pass lung uptake of ^{123}I-IMP was reported to be 0.92 ± 0.4 using a multiple indicator dilution technique 14). Although high first-pass lung uptake of ^{123}I-IMP was indicated, this

assumption did not seem to be valid 12). On the other hands, some indices of ^{123}I-IMP lung clearance correlated well with those of arterial input function 12) and brain uptake15). The rCBF can be easily calculated by means of microsphere model analysis if the AIF(T) could be estimated from the TCL(T) values. The aim of this study was to evaluate the relationship between AIF(T) and TCL(T) values using the graph-plot analysis and establish a method to estimate AIF(T) from TCL(T) values.

Materials and Method

Theory

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

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

where Cb(T)(μCi/g) is regional radioactivity of the brain tissue at T minutes after an injection of the ^{123}I-IMP, and Ca(t)(μCi/ml) is the radioactivity-time course of the ^{123}I-IMP in arterial blood, and $\int Ca(t)dt$(min*μCi/ml) is the integral of arterial input function during T minutes(AIF(T)).

From the peak radioactivity of the lung(L_{peak}) and radioactivity of the lung at T minutes(L(T)), TCL(T) is calculated as follows,

$$TCL(T)=L_{peak}-L(T) \quad (2)$$

If the AIF(T) can be estimated from the TCL(T), $\int Ca(t)dt$ can be replaced estimated AIF(T). Therefore, rCBF can be calculated non-invasively by using the microsphere model with ^{123}I-IMP as follows,

$$rCBF=Cb(T)/\text{estimated AIF(T)} \quad (3)$$

We hypothesized that AIF(T) directly reflects to the clearance of ^{123}I-IMP from the lung. TCL(T) is estimated by the exponential fitting of the time-activity curve of the lung(12). We hypothesize that a linear relationship is present between the value of AIF(T) and TCL(T)(Fig. 1). Then, AIF(T) can be estimated from the following equation,

$$AIF(T)=aTCL(T) + b \quad (4)$$

The constant of a and b can be estimated by the linear regression analysis. This is a method for transformation of TCL(T) into AIF(T) by using graph plot(transformation by graph plotting method: T-plot).

Patients

Ten consecutive patients (age: 71.1 $\pm$ 4.9 years, male/female: 7/3) with a cerebral infarction were prospectively enrolled in this study(Table 1). There were not any lung diseases in all patients. As all patients were studied four times during the course of clinical follow-up, 40 studies were included in this study. We excluded 3 studies because of the continuous blood sampling failure. Therefore, total of 37 studies in 10 patients were included in this study. We divided the 37 studies into 2 groups. The

first 10 studies in each patient were analyzed in comparison with the continuous ABS counts in octanol fraction to derive equations for estimation yielding an accurate AIF(5) from the chest dynamic planar imaging data(Fig. 1). AIF(5) was correspond to the AIF(T) collected from 0 to 5 min. after injection of ^{123}I-IMP. The subsequent 27 studies served to confirm the validity of proposed method with the equations for estimation of AIF(5). The study was performed according to the guidelines of the ethical committee of our institution, and all patients gave written informed consent.

General procedure

We used a two-head gamma camera (Millennium VG, GE,) equipped with a low-energy general-purpose collimator. Patients underwent a dymanic planar imaging of the chest with anterior view for 3 minutes(1sec/frame for 60 seconds and 10 sec/frame for 120 seconds, 128x128 matrix) after a bolus injection of ^{123}I-IMP. The bolus injection was performed in 7 studies via the right arm veins(RA group) and 30 studies via the left arm veins(LA group). After the dymanic planar imaging of the chest, patients were moved to set for the brain imaging. Planar imaging of the brain (Cb5) was obtained at 5 minutes after the bolus injection of ^{123}I-IMP for 1 minute (128x128 matrix). Planar imaging of the brain were also obtained before (Cbpre) and after (Cbpost) a SPECT imaging of the brain. SPECT imaging of the brain was performed at 15 minutes after the bolus injection of ^{123}I-IMP for 20 minutes (continuous mode, 60 steps, 20 sec/a step, magnification 1.5x, 128x128 matrix). Axial SPECT images were reconstructed with filtered backprojection method using a Ramp filter. Butterworth filter of order 10 and cut-off 0.45 was used for a pre-reconstruction filter. Reconstructed slice thickness was 2.95 mm. Attenuation correction and scatter correction were not performed. We loaded ^{123}I-IMP (167MBq in 1.5 ml) in an extension tube connected to a 20ml/syringe in advance and injected it as a bolus into a vein of the right or left arms in 10 seconds with 20 ml of saline.

Continuous ABS

Continuous ABS was performed with a withdrawal pump from a 27-gauge Teflon catheter placed in the right radial artery through an extension tube. The total dead space for sampling was about 1 ml. Continuous sampling at a constant speed of 1 ml/min was started immediately after the bolus injection of ^{123}I-IMP and stopped 5 minutes after injection of ^{123}I-IMP. Total radioactivity of the blood sample(1 ml: whole blood counts) was measured by a scintillation well counter immediately after the continuous arterial blood sampling. The mixture of 0.5 ml of sampling blood and 2 ml of octanol was shaken by a vortex and centrifuged at 3000 RPM for 20 min. The radioactivity of 1.0 ml of the octanol fraction(octanol counts) was measured by a

scintillation well counter. Then AIF(5) was obtained by the following equation:

AIF(5)=4x(octanol counts/whole blood counts)x whole blood counts(counts/ml)

Estimation of an input function from a time-activity curve of the lung.

A large region of interest(ROI) covering both lung fields were set to obtain a curve for clearance of ^{123}I-IMP from the lungs(Fig. 2A). The planar imaging of the brain at 5 min (Cb5) was necessary for the measurement of rCBF. Thus, the patient's table moved from the chest position and set for imaging the brain till 5 min. after the injection of ^{123}I-IMP. Therefore, we used an extrapolated lung clearance curve obtained by fitting a downward slope of the curve from 1 min to 3 min after injection of ^{123}I-IMP with a mono-exponential curve(Fig. 2B). The value of L(5) was estimated from this curve and TCL(5) was calculated by the following equation : $TCL(5)=L_{peak}-L(5)$.

Correction factor for the count loss of collimator and cross calibration factor of counts on planar image to the radioactivity in the pool phantom were obtained. Then, TCL(5) was converted to the radioactivity using both factors.

Regression analysis for the estimation of AIF(5)

To assess the feasibility of our theory, a linear regression analysis was performed between the value of AIF(5) and TLC(5) in all studies.

Validation of the method

Regression equation was obtained from the first 10 studies in each patient for the estimation of AIF(5). The validity of the proposed method was evaluated in the other 27 studies. Estimated AIF(5) was calculated from the regression equation determined by the regression analysis of the first 10 studies. Then, the linear regression analysis was performed between the AIF(5) and estimated AIF(5). The reproducibility of this method was also evaluated using a correlation of variance(CV) of all studies performed in each patient. We compared mean CV of measured AIF(5) with that of estimated AIF(5) in all patients.

Statistics

MedCalc software was used for the analysis. A paired t-test was performed in the comparison of mean CV between measured AIF(5) and estimated AIF(5). Statistical significance was defined as p-value of less than 0.01.

Results

Regression analysis for the estimation of AIF(5)

AIF(5) was correlated well with TCL(5) in all studies($r=0.81$, $p<0.0001$, Fig. 3). The method to estimate the AIF(5) by means of using a regression equation between the measured AIF(5) and TCL(5) was feasible.

Validation of the method

In the first 10 studies of each patient, good linear correlation was obtained between the AIF(5) and TCL(5)(Fig. 4). They underwent the bolus injection via the left arm veins. The regression equation for the estimation of the AIF(5) was derived as follows,

Estimated AIF(5)=4.1735xTCL(5) + 2146.7336(r=0.94, p=0.0001).

In the rest of 27 studies, good linear correlation was obtained between measured AIF(5) and estimated AIF(5)(r=0.79, $p<0.0001$, Fig. 5). There was a significant difference in mean value of TCL(5) between the bolus injection via the right arm vein and that via the left arm vein($p< 0.01$)(Fig. 6). In 20 studies performed the bolus injection via the left arm veins except for the first 10 studies, good correlation was obtained between the estimated AIF(5) and measured AIF(5)(r=0.83, $p<0.0001$; Fig. 7). Good correlation was also present between the mean right hemispheric rCBF using the measured AIF(5)(microsphere) and that using the estimated AIF(5) (T-plot)(r = 0.76, $P<0.001$; Fig. 8).

Reproducibility of estimated AIF(5)

Mean CV of measured AIF(5) and estimated AIF(5) was 12.5 % and 17.0 %, respectively. There was significant difference was not present between them($p=0.26$).

Discussion

In the present study, we hypothesized that the ^{123}I IMP activity in the arterial blood directly reflected the ^{123}I IMP activity released from the lung parenchyma. To confirm the feasibility of our theory, the relationship between AIF(5)(total ^{123}I IMP activity in octanol fraction of the arterial blood sampling for 5 min.) and TCL(5)(total ^{123}I IMP activity released from the lungs during 5 min.)after the injection were analyzed by graph plot. Good linear correlation was obtained between the AIF(5) and TCL(5) by regression analysis. This result shows our theory is reasonable. Therefore, AIF(5) was considered to be estimated from the TCL(5) by using a T-plot. Qualitative CBF measurement using ^{123}I-IMP SPECT can be performed basis on the microsphere model without any blood sampling using the T-plot.

To verify this method, T-plot was performed in the first 10 studies in each patient and the regression equation was obtained. Then, estimated AIF(5) was obtained in other 27 studies by using this equation. There was significant correlation between the measured and estimated AIF(5). Bolus injection was performed via the left arm veins in the first 10 studies for T-plot. On the other hands, 7 of other 27 studies were performed bolus injection via the right arm veins. The TCL(5) was significantly higher in studies with bolus injection via the right arm veins than those via the left arm veins. In 20 studies with bolus injection via the left arm veins,

correlation between measured and estimated AIF(5) was improved from 0.79 to 0.83. Therefore, higher TCL(5) in bolus injection via the right arm veins results in the overestimation of estimated AIF(5) in the 27 studies. Nishizawa et al.(12) reported that peak counts of the lung would be affected by how rapidly the tracers was given as a bolus. Thus, the difference in the TCL(5) in two groups is considered to reflect the difference in the quality of bolus injection between the right arm veins and the left arm veins. The quality of bolus injection via the right arm veins is superior to that via the left arm veins because of shorter distance from the injected veins to the heart via the right arm veins. Although the methods used as a gold standard are different , the values of correlation coefficient between the measured and estimated AIF(5) are compatible to those of previously reported 9)12). We derived the equation from the first 10 studies of each patient to correct AIF(5) obtained from the TCL(5) by T-plot. This equation worked well in the other studies excluding 7 studies with bolus injection via the right arm veins.

The reproducibility of estimated AIF(5) is not different from that of measured AIF(5). Although another T-plot is necessary to estimate AIF(5) in the studies with bolus injection via the right arm veins, this method is considered to be useful for the quantification of rCBF without any blood sampling.

There are some advantages of this method as compared the noninvasive methods previously proposed 9)-12). In the autoradiography(ARG) method9-10), AIF derived from a standard input function defined by one ABS was used for the measurement of CBF. Therefore, the difference in AIF of each patient was ignored. On the other hands, AIF(5) of each study could be estimated by the T-plot. The NIMS method is also proposed for the measurement of CBF as a noninvasive method without any blood sampling11)-13). It requires calculation of the residual radioactivity in the syringe, continuous acquisition of chest and head images with SPECT in addition to planer images of both structures, determination of CO from the TAC of the right heart system, and the calculation of the cross calibration factor between planar and SPECT images. The calculation of the residual radioactivity and determination of CO are not necessary for the measurement of CBF using the T-plot proposed in the present study. There are more factors inducing errors in the measurement of CBF using NIMS method as compared with the T-plot12). The new quantification method performed in the present study, which uses ^{123}I-IMP and graph plot analysis, is simple and convenient.

Clearance of ^{123}I-IMP in the lung is affected by the lung disease, although lung diseases were not present in all patients in this study. Our theory is based on the

assumption that brain accumulation is proportional to the clearance of ^{123}I-IMP from the lungs. Therefore, change in the clearance of ^{123}I-IMP from the lungs is not considered to affect the estimation of TLC(5) in patients with lung diseases.
However, additional study in these patients is necessary.

Although the measurement of rCBF may not be necessary for many patients, it is informative for the management of patients with cerebrovascular disease, 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 12).
Therefore, this noninvasive method is recommended as an alternative to the invasive method using ABS.

There are some limitations present in the present study. First, we estimated L(5) from the time-activity curve of the lung obtained from 0 to 3 min. after injection of ^{123}I-IMP instead of direct measurement of L(5). Same estimation was performed in other literatures 11-12, 15). However, further study is necessary to validate the feasibility of these estimation methods. Second, the values of CBF have not been calculated. The errors in the values of CBF is predicted to indicate the same errors observed in the values of estimated AIF(5), because the estimated AIF(5) is used for the measurement of CBF instead of the measured AIF(5) using the same equation proposed by Kuhl DE. et al. 2) Third, validation of our method have been performed the studies of same patient population. However, each study is independently performed. Therefore, this method is feasible to use in the different patient population as well. Fourth, attenuation and scatter corrections were not performed in this study. These corrections will be necessary for more accurate quantification of CBF in the future. Finally, T-plot has not been performed and validated in the studies injected of ^{123}I-IMP via the right arm veins because of its small number of studies. Good correlation was obtained between the TCL(5) and measured AIF(5) in all studies. Therefore, T-plot is also useful to perform in the study injected ^{123}I-IMP via the right arm veins. Further study is necessary to confirm the feasibility of T-plot in using the study injected ^{123}I-IMP via the right arm veins.

In conclusion, it is feasible to use the estimated AIF(5) by using the T-plot for the measurement of CBF on the basis of the microsphere model instead of the measured AIF(5). CBF can be measured by adding the dynamic planar imaging of the chest to the imaging protocol on the basis of the microsphere model without any blood sampling. T-plot has the potential value for measuring CBF noninvasively using ^{123}I-IMP.

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Figure legends

Fig. 1 Schematic display of time-activity curve of the lungs and arterial blood. Total counts in the arterial blood sampling for T minutes(AIF(T)) is proportional to the total counts cleared from the lung between peak time(Lpeak) and T minutes(L(T)) after a bolus injection of ^{123}I-IMP(TCL(T)) .

Fig. 2 A: ROI for time–activity curve of the lung. B: An example of the time–activity curve for ROI of the lung. Green line indicates measured time– activity of the lung. Red line represents the peak counts (L_{peak}) and yellow line shows the fitted line by using a monoexponential curve. The lung counts of 5 min after the injection of ^{123}I-IMP (L(5)) is estimated by this yellow line.

Fig. 3 Correlation between measured AIF(5) and TCL(5) in all studies.

Fig. 4 Correlation and regression equation between measured AIF(5) and TCL(5) in the first 10 studies of each patient for transformation of TCL(5) into estimated AIF(5).

Fig. 5 Correlation between measured AIF(5) and estimated AIF(5) determined by T-plot in other 27 studies.

Fig. 6 Comparison of TCL(5) between studies injected via the left arm veins(left side) and those via the right arm veins(right side). Mean values of TCL(5) are significantly different in 2 groups by unpaired t-test.

Fig. 7 Correlation between measured AIF(5) and estimated AIF(5) determined by T-plot in 20 studies performed bolus injection via the left arm veins.

Fig. 8 Correlation between mean right hemispheric cerebral blood flow using measured AIF(5) (microsphere) and that using estimated AIF(5) determined by T-plot (T-plot) in 20 studies performed with bolus injection via the left arm veins

Table 1 Characteristics of patients

Case No.	Age	Sex	Stroke type	MVL	No. of exam.
1	62	male	lacunar	none	4(1)*
2	78	male	cardioembolic	none	4
3	70	male	atheroembolic	none	4
4	72	male	lacunar	none	4
5	79	female	BAD	Lt. MCA	4(2)*
6	70	male	lacunar	none	4
7	68	male	atheroembolic	Rt. MCA	4
8	73	female	aortogenic	none	4
9	70	female	cardioembolic	Lt. MCA	4
10	69	male	atheroembolic	Lt. MCA	4

*Number in parenthesis represents number of continuous arterial blood sampling failure

Note: No.; number, CI; cerebral infarction, MVL; major vessel lesion, exam.; examination, BAD; branch atherosclerotic disease, MCA; middle cerebral artery