Evaluation of an automatic non-invasive quantitative measurement method of the regional cerebral blood flow using $^{99m}$Tc-ECD brain uptake ratio

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Aims and objectives

Quantitative measurement of cerebral blood flow is important for objective evaluation of cerebral hemodynamic status [1]. $^{123}\text{I}$-N-isopropyl-$p$-iodoamphetamine ($^{123}\text{I}$-IMP), $^{99m}\text{Tc}$-D, $^{99m}\text{Tc}$-HMPAO, and $^{99m}\text{Tc}$-ethyl cysteinate dimer ($^{99m}\text{Tc}$-ECD) have been widely used for quantitative measurement of regional cerebral blood flow (rCBF) by single photon emission computed tomography (SPECT) [2-4]. The method of continuous arterial blood sampling on a microsphere using $^{123}\text{I}$-IMP SPECT (IMP-MS) and the auto-radiographic method with one-point arterial blood sampling using $^{123}\text{I}$-IMP SPECT (IMP-ARG) have mainly been used for measurement of rCBF in routine clinical study [5-7].

Several non-invasive quantitative measurement methods without any arterial blood sampling have been proposed using $^{123}\text{I}$-IMP, $^{99m}\text{Tc}$-ECD, and $^{99m}\text{Tc}$-HMPAO SPECT [8-12]. Non-invasive quantitative measurements are useful for clinical study because these methods have simple and pain-free procedures [13-15].

A new non-invasive quantitative measurement method, the improved brain uptake ratio (IBUR) method using $^{99m}\text{Tc}$-ECD SPECT, has recently been reported [16]. This method changed the location of the ROI from the aortic arch to the ascending aorta (based on arterial blood flow dynamics) in order to obtain an accurate input function [17]. Furthermore, the regression equation for the IBUR method was constructed based on $\text{H}_2\text{O}^{15}$-positron emission tomography ($\text{H}_2^{15}\text{O}$-PET) as a gold standard [17]. For these reasons, the rCBF values obtained by the IBUR method can be evaluated in the same way as the rCBF values obtained by the $\text{H}_2^{15}\text{O}$-PET method.

The patlak plot (PP) method using $^{99m}\text{Tc}$-ECD is widely used in clinical study in japan [11, 14,15]. Clarifying the difference of rCBFs obtained by the PP and IBUR method is important for clinical diagnosis during the transition period of the method.

The purpose of this study is to demonstrate the relation of rCBF obtained by the IBUR and PP method, and to indicate the usefulness of the IBUR method in the clinical study.
Methods and materials

Subjects

The images of 16 consecutive patients (11 men, 5 women; age, 52-85 years; mean age, 71 years) who underwent both $^{99m}$Tc-ECD chest RI angiography and SPECT examinations at National Hospital Organization Kyushu Medical Center. None of the patients had pulmonary disease. The studies were approved by the institutional ethics boards of each participating institution, and written informed consent was obtained from all patients or their next of kin.

$^{99m}$Tc-ECD imaging

$^{99m}$Tc-ECD imaging was performed at each of the facilities using a dual-head SPECT scanner (E-cam, Siemens, Germany). $^{99m}$Tc-ECD RI angiography of the anterior brain and chest at a 15° left-anterior-oblique (LAO15) view were simultaneously obtained for 2 min (1 s/frame, 128 × 128 matrix) using a detector equipped with low energy high resolution (LEHR) collimators and a 140 keV ±7.5% energy window after a bolus injection of 600 MBq of $^{99m}$Tc-ECD. The pixel size was 4.00 mm. The LAO 15 position of the chest was obtained by modifying the body. The head position was fixed at the anterior position at this time.

After $^{99m}$Tc-ECD chest RI angiography, SPECT was performed at 30 min mid-scan time. The projection data were acquired every 150 s by continuously rotating the detectors by 180 degrees (60 steps/180 degrees/150 s, 128 × 128 matrix).

The SPECT images were obtained using the 2-dimensional ordered subset expectation maximization (2D-OSEM) method (subsets; 5, iterations; 20). These counts of the 2D-OSEM method were directly proportional to the counts that had been obtained by the filtered back projection method. An attenuation coefficient of 0.09 cm$^{-1}$ and a Butter-worth pre-filter (cutoff; 0.5 cycle/cm, order; 8) were used for image reconstruction.

CBF analysis

Patlak-plot (PP) method

A count-time activity curve (TAC) for the arterial input function of the RI angiography images was obtained by setting circular ROIs with a diameter of 4 pixels on the ascending aorta as an input function, and cerebral hemisphere ROIs on the anterior brain as output functions [11,14,15]. The location of the ROI was manually determined by identifying the all dynamic images. The Brain perfusion index (BPI) was obtained by analyzing the TACs
of the aortic arch and the normal side brain. Finally, the mCBF was calculated by using
the $^{133}$Xe regression equation [14] (Fig. 1).

The Syngo MI Applications VA46B Brain Patlak Proc. program (Siemens, Germany) was
used for the analyzing of the PP method.

The rCBF of each region was calculated by converting the integrated SPECT counts of
the basal ganglia to mCBF.

**IBUR method**

A count-time activity curve (TAC) for the arterial input function of the dynamic images
was obtained by setting circular ROIs with a diameter of 4 pixels on the ascending aorta
based on the blood flow dynamics [18, 19]. The location of the ROI was automatically
determined by identifying the region with the maximum counts in the ascending aorta
among all dynamic images. The second peak of the TAC was fitted with the gamma
function, because the first peak indicated the pulmonary artery or lung activity which
overlaps to the ascending aorta. The input counts were obtained by integrating their
gamma functions. The SPECT counts were converted using the Lassen's correction [20].
The regional brain uptake ratio BUR (rBUR) was directly obtained by dividing the SPECT
counts of the same region by the input function and multiplying by the cross calibration
factor (CCF) between the planar image counts and SPECT image counts. Finally, the
rCBF was calculated by using the $H_2^{15}$O PET regression equation (Fig. 2). The process
from the setting of the ROI in the dynamic images to the calculation of the rCBFs was
automatically performed with an original analyzing software using C++.

The mCBF was calculated by averaging the rCBF values of the the basal ganglia.

**PP vs IBUR**

All SPECT and PET images were analyzed using a three-dimensional stereotaxic ROI
template (3DSRT) on anatomically standardized CBF SPECT images to objectively
estimate the rCBF [21]. The 3DSRT is composed of 259 ROIs in 11 segments (1:Anterior,
2:PreCentral, 3:Central, 4:Pariental, 5:Angular, 6:Temporal, 7:Occipital, 8:PeriCallosal,
9:Lenticular Nuc, 10:Thalamus, 11:Hippocampus, 12:Cerebellum:) on each side. The
rCBF values were obtained using the 3DSRT (Fig. 3). In addition, 12 ROIs in 6 segments
(1:Cornu frontale ventriculi lateralis, 2:Pars centralis ventriculi lateralis, 3:Atrium) were
set on the lateral ventricles. The area-weighted average (segmental CBF; sCBF) of the
28 segments based on the sCBF in each ROI was calculated using the sCBF. In this
study, the sCBF and sCBF were defined as rCBF and rBUR, respectively.

The correlation between the BUR values obtained by the IBUR method and the BPI
values obtained by the PP method was determined by linear regression analysis. The
mCBF and rCBF values of the IBUR method were compared with values obtained by the PP method.
**Fig. 1:** Scheme of the Patlak plot (PP) method. In the patlak plot method, a ROI set of the aortic arch ROI by in order to obtain input function. 2ROIs are set on Left and right brain. Brain perfusion index (BPI) are obtained by analyzing the time activity curves (TAC) of aortic arch and brain ROI. Mean CBF are obtained by using the $^{133}$Xe regression equation.

$^{133}$Xe-mCBF = 2.60 × (BPI) + 19.8

Whole brain CBF (mCBF) using $^{133}$Xe regression equation

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**Fig. 2:** Scheme of the IBUR method. In the IBUR method, the location of the region of interest (ROI) is set on the ascending artery in order to obtain an accurate input function. We obtained Brain uptake ratios (BUR) of regional SPECT counts. rCBFs are obtained by using the H215O PET regression equation.

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Fig. 3: Regions of interest in image slices standardized using 3-dimensional stereotactic surface templates (3DSRT) The 3DSRT is composed of 24 ROIs in 12 segments (1: Anterior, 2: Precentral, 3: Central, 4: Pariental, 5: Angular, 6: Temporal, 7: Occipital, 8: Pericallosal, 9: Lenticular Nuc, 10: Thalamus, 11: Hippocampus, and 12: Cerebellum) on each side.

Results

Figure 4 shows the correlation between the BPI of the PP method and BUR of the IBUR method. The BUR values obtained using the IBUR method increased linearly as the BPI increased.

The regression equation for the BUR was expressed as

\[ \text{BUR} = 1.12 \times \text{BPI} \quad (r = 0.75, \ p<0.05) \quad (1). \]

A well correlation was found between the BUR values measured by the IBUR method and the BPI values by the PP method. The range of the BUR values was from 4.4 to 13.6, and that of the PP values was from 5.7 to 10.9, respectively. The range of the IBUR method indicated 2 times wide range to the PP method.

Figure 5 shows the linear regression analyses for mCBF measurements by the PP and BUR methods. Individual mCBF values obtained using these independent techniques were found to be well correlated \((r = 0.73, \ p<0.001)\). The IBUR flow range was found from 18.8 to 48.5 ml/100g/min, and the PP flow range was found from 34.7 to 48.5 ml/100g/min.

Figure 6 shows the linear regression analyses for rCBF measurements by the PP and BUR methods. Individual rCBF values obtained using these independent techniques were found to be well correlated \((r = 0.75, \ p<0.001)\). The IBUR flow range was found from 16.3 to 60.1 ml/100g/min, and the PP flow range was found from 26.7 to 58.8 ml/100g/min.

Table 1 compares the mean and regional CBF between the PP and IBUR methods.

The maximum mCBF and rCBF of the IBUR method were approximately equal to the PP method.

The minimum mCBF and rCBF of the IBUR method were 54% and 40% lower than the PP method respectively.
Fig. 4: Correlation between BPI (PP method) and BUR (IBUR method) The range of the BUR values was from 4.4 to 13.6, and that of the PP values was from 5.7 to 10.9, respectively.

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Fig. 5: Correlation between PP and IBUR (mCBF) The regression equation of the mCBF was expressed as $Y = 1.37x - 23.0$ ($r = 0.73$, $p<0.0001$). IBUR flow range was found from 18.8 to 48.5 ml/100g/min, and PP flow range was found from 34.7 to 48.5 ml/100g/min.

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Fig. 6: Correlation between PP and IBUR (rCBF) The regression equation of the rCBF was expressed as $Y = 1.06x - 6.1$ ($r = 0.75$, $p<0.0001$). IBUR flow range was found from 16.3 to 60.1 ml/100g/min, and PP flow range was found from 26.7 to 58.8 ml/100g/min.

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Table 1: Comparison of CBF range between the PP and IBUR methods. The maximum CBFs of the IBUR method were approximately equal to the PP method. The minimum rCBF of the IBUR method were 40% lower than the PP method.

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Conclusion

In an adult, CBF is typically 750 ml/min or 15% of the cardiac output and this equates to 50 to 54 ml/ g/min [23]. CBF is tightly regulated to meet the brain's metabolic demands [23]. The higher CBF (a condition known as hyperemia) can raise intracranial pressure (ICP), which can compress and damage delicate brain tissue. The lower CBF (ischemia) results if blood flow to the brain is below 18 to 20ml/100g/min, and tissue death occurs if flow dips below 8 to 10 ml/100g/min [23] . The diagnosis of a low CBF region is important in neurosurgery and neurology. In this study, the rCBF range from 16.3 to 60.1 ml/100g/min was detected using the IBUR method. This means the ischemia and tissue death can be detected by the IBUR method. However, the ischemia cannot be detected by the PP method by underestimation. Thus, the PP method should not use for the lower rCBF diagnosis. Ito et al. reported that the rCBF diagnosis using the IBUR method can be performed equivalent to the H$_2^{15}$O PET method. Additionally, the results indicated that the lower rCBF can be detected by the IBUR method.

Therefore, the IBUR method is more useful than the PP method for the clinical diagnosis.
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