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Error analysis of measured cerebral vascular response to acetazolamide stress by I-123-IMP autoradiographic method with single photon emission computed tomography: Errors due to distribution volume of I-123-IMP

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Objectives: Iodine-123 (^{123}I)-labeled *N*-isopropyl-*p*-iodoamphetamine (IMP) has been used as a cerebral blood flow (CBF) tracer for single-photon emission computed tomography (SPECT), and measurements of the CBF response to acetazolamide stress by SPECT with IMP are widely used to assess cerebral vascular reserve. To quantitate CBF by means of SPECT with IMP, an autoradiographic (ARG) method has been developed and is widely used. In the ARG method, CBF is calculated from the brain counts of the SPECT scan with an assumed distribution volume value of IMP (V_d). However, differences between true V_d and assumed V_d results in errors in calculated CBF. In the present study, errors in the CBF response to acetazolamide stress as calculated by the ARG method were investigated. ***Methods:*** SPECT studies were performed on 12 patients with steno-occlusive lesions of the major cerebral artery. Two studies were performed on separate days. The first study was performed at rest (baseline), and the second during acetazolamide stress. SPECT scans were performed at 40 min (early scan) and 180 min (delayed scan) after intravenous injection of IMP. ***Results:*** Although a simulation study showed that errors in calculated changes in CBF in response to acetazolamide stress, which result from differences between the true V_d and the assumed V_d, were larger when the baseline CBF and change in CBF were larger, values calculated by the ARG method with an assumed V_d were in good agreement with those calculated with true V_d obtained from early and delayed scan data. ***Conclusion:*** These data indicate that errors in the calculated CBF response to acetazolamide stress as calculated by the ARG method are negligible even at high CBF responses. The ARG method is therefore reliable for measurement of CBF response to acetazolamide stress.

Key words: IMP, SPECT, acetazolamide, cerebral vascular reserve, ARG method

INTRODUCTION

Iodine-123 (^{123}I)-labeled *N*-isopropyl-*p*-iodoamphetamine (IMP)[1,2] has been used as a cerebral blood flow (CBF) tracer for single-photon emission computed tomography (SPECT) to investigate the pathophysiology of several brain diseases, particularly occlusive cerebrovascular disease.[3,4] Decreased cerebral perfusion pressure due to major cerebral arterial occlusive disease causes cerebral autoregulatory vasodilatation to maintain CBF (stage I hemodynamic change).[5] Decreased cerebral perfusion pressure below the lower limit of cerebral autoregulation causes a decrease in CBF with an increased cerebral oxygen extraction fraction (OEF) for maintenance of the cerebral metabolic rate of oxygen ($CMRO_2$) (stage II hemodynamic change).[5] For assessment of stage I

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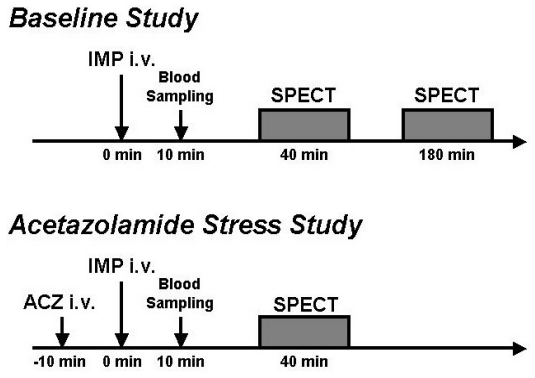

Fig. 1 Schema of protocol for SPECT studies under baseline and acetazolamide stress conditions.

hemodynamic compromise, the CBF response to acetazolamide stress is measured by SPECT as an indicator of cerebral vascular reserve. Reduced vasodilatory capacity as determined by the acetazolamide stress test is a major predictor of stroke recurrence.[6,7]

To quantitate CBF by IMP and SPECT, an autoradiographic (ARG) method has been developed,[8–10] and is used widely to measure the CBF response to acetazolamide stress.[11] In the ARG method, CBF is calculated from the brain counts of the SPECT scan with an assumed distribution volume value of IMP (V_d). Because CBF calculated by the ARG method is dependent on assumed V_d values,[8,9] the V_d value should conceivably be determined for each SPECT scanner system by a table look-up (TLU) method[9] that calculates CBF and V_d from 2 types of SPECT scan data (early scan and delayed scan).[12,13] However, differences between true V_d and assumed V_d result in errors in calculated CBF, and this error is greater when the CBF is high, for example, during acetazolamide stress.[8,9] In the present study, we evaluated errors in the CBF response to acetazolamide stress as calculated by the ARG method and which are caused by differences between the true V_d and assumed V_d.

MATERIALS AND METHODS

Subjects

SPECT studies were performed on 12 patients (7 men and 5 women, mean age ± SD: 61 ± 21 years, age range: 20–82 years) with steno-occlusive lesions of the major cerebral artery, including moyamoya disease. Magnetic resonance imaging (MRI) and angiography or MR angiography were performed on all patients. All patients were chronically ill.

SPECT procedures

Two SPECT studies were performed on separate days (Fig. 1). The first study (baseline) was performed at rest, and the second during acetazolamide stress. The interval between the 2 studies was 2–7 days. For the baseline study, 2 SPECT scans were performed at 40 min (early scan) and 180 min (delayed scan) of mid-scan time after intravenous infusion of 111 MBq IMP for 1 min. For the acetazolamide stress study, 1 SPECT scan was performed at 40 min of mid-scan time after intravenous infusion of 111 MBq IMP for 1 min. Acetazolamide (1 g) was administered intravenously for 1 min starting 10 min before the beginning of IMP infusion. One-point arterial blood sampling from the brachial artery was performed at 10 min after IMP infusion to measure radioactivity concentration of whole blood and arterial blood gases. The SPECT scan protocol acquired 64 projections at 25 sec (25 sec × 4 head camera = 100 sec total) per projection with 360° continuous rotation of the camera. A SPECT scanner (SPECT-2000H, Hitachi Medico Corp., Tokyo, Japan),[14] with a 4-head rotating gamma camera fitted with low-energy, medium-resolution collimators and in-plane and axial resolutions of 10 mm full width at half maximum (FWHM), was used for all measurements. Image reconstruction was performed by filtered backprojection with a Butterworth filter, and attenuation correction was made numerically by assuming the object shape to be an ellipse for each slice and the attenuation coefficient to be uniform (0.08 cm^{-1}).[15,16] Correction for scattered photons was not performed. Image slices were set up parallel to the orbito-meatal (OM) line and were obtained at 8-mm intervals through the whole brain. A cross calibration scan was performed using a 16 cm in inner diameter cylindrical uniform phantom for calibrating sensitivity between the SPECT scanner and the well counter system.

Data analysis

Regions of interest (ROIs) were drawn on all SPECT images. Elliptical ROIs (16 mm × 32 mm) were defined bilaterally for the cerebrocortical region as the area of the middle cerebral artery on a slice at the level of the centrum semiovale. CBF and V_d were calculated for each ROI by the TLU and ARG methods. In the ARG method, CBF is calculated from the brain counts of early scan with an assumed V_d. In the TLU method, CBF is calculated with true V_d obtained from early and delayed scan data. The arterial input function is determined by calibration of the standard input function with one-point arterial blood sampling at 10 min after IMP infusion in both methods.

For the baseline study, CBF and V_d were calculated by the TLU method ($CBF_{baseline\text{-}TLU}$). Baseline CBF was also calculated by the ARG method with the average V_d value of 12 patients ($CBF_{baseline\text{-}ARG}$). For the acetazolamide stress study, CBF was calculated by the ARG method with V_d values for each ROI obtained from the baseline study with the TLU method ($CBF_{ACZ\text{-}TLU}$). CBF in response to acetazolamide stress was also calculated by the ARG method with average V_d values of 12 patients obtained from the baseline study with the TLU method ($CBF_{ACZ\text{-}ARG}$). The CBF response to acetazolamide stress was calculated as percent change:

Table 1 P_aCO_2, P_aO_2 and pH in SPECT studies

Study	P_aCO_2 (mm Hg)	P_aO_2 (mm Hg)	pH
Baseline	41.3 ± 2.8	87.7 ± 11.0	7.411 ± 0.018
Acetazolamide stress	41.0 ± 3.0	93.1 ± 9.0	7.412 ± 0.019

Values are shown as mean ± SD

$$\% \text{ change in } CBF_{TLU} = 100 \cdot (CBF_{ACZ\text{-}TLU}/CBF_{baseline\text{-}TLU} - 1)$$
$$\% \text{ change in } CBF_{ARG} = 100 \cdot (CBF_{ACZ\text{-}ARG}/CBF_{baseline\text{-}ARG} - 1)$$

Simulation study

In the ARG method, differences in regional V_d from assumed V_d result in errors in the estimated CBF.[8,9] To estimate errors in changes in CBF in response to acetazolamide stress as calculated by the ARG method, a simulation study was performed. The brain radioactivity curve was generated for a CBF range of 0–100 m*l*/100 m*l*/min according to the standard two-compartment model[12] where the V_d values were assumed to be 31–47 m*l*/m*l* in 9 steps. The standard input function used in the TLU and ARG methods was employed for the arterial input function.[12] For each calculated brain radioactivity curve, the CBF was calculated by the ARG method with an assumed V_d value of 39 m*l*/m*l*. Changes in the CBF in response to acetazolamide stress were then calculated from these calculated CBF values assuming a baseline CBF of 20–50 m*l*/100 m*l*/min in 4 steps. Calculated changes in CBF then were compared to assumed changes in CBF.

RESULTS

P_aCO_2, P_aO_2 and pH in each SPECT study are shown in Table 1. No significant differences were observed between the studies.

The simulation study showed that errors in V_d compared to assumed V_d in the ARG method of −20% to 20% resulted in errors in CBF of −6% to 5% and −12% to 9% for true CBF values of 30 and 50 m*l*/100 m*l*/min, respectively (Fig. 2). In the measured data, CBF_{ARG} ($CBF_{baseline\text{-}ARG}$ and $CBF_{ACZ\text{-}ARG}$) was in good agreement with CBF_{TLU} ($CBF_{baseline\text{-}TLU}$ and $CBF_{ACZ\text{-}TLU}$) (Fig. 3). Average values (± SD) of $CBF_{baseline\text{-}ARG}$, $CBF_{ACZ\text{-}ARG}$, $CBF_{baseline\text{-}TLU}$, and $CBF_{ACZ\text{-}TLU}$ were 32.7 ± 7.5, 46.4 ± 11.1, 31.6 ± 6.5, and 46.5 ± 10.8 m*l*/100 m*l*/min, respectively. The average V_d value (± SD) as calculated by the TLU method in the baseline study was 38.7 ± 3.9 m*l*/m*l*.

Results of simulation studies of errors in changes in CBF in response to acetazolamide stress as calculated by the ARG method are shown in Figure 4. When the baseline CBF and change in CBF were larger, errors in changes in CBF (those caused by errors in V_d compared to assumed V_d in the ARG method) were larger. When the baseline CBF was 30 m*l*/100 m*l*/min, errors in V_d of −20% to 20% resulted in errors in changes in CBF of −13% to 9%, while the true change in CBF was 50%.

In the measured data, percent change in CBF_{ARG} was in good agreement with percent change in CBF_{TLU}, although the percent change in CBF_{ARG} was −12% less than the percent change in CBF_{TLU} on average (Fig. 5). Average values (± SD) of percent change in CBF_{ARG} and in CBF_{TLU} were 42.7% ± 22.8% and 48.4% ± 24.8%, respectively.

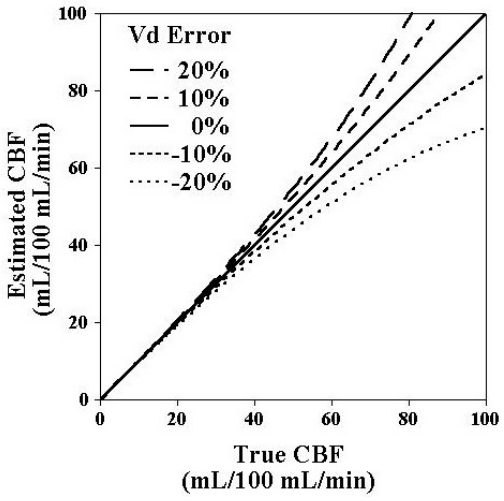

Fig. 2 Errors in CBF as calculated by ARG method with errors in V_d compared to assumed V_d.

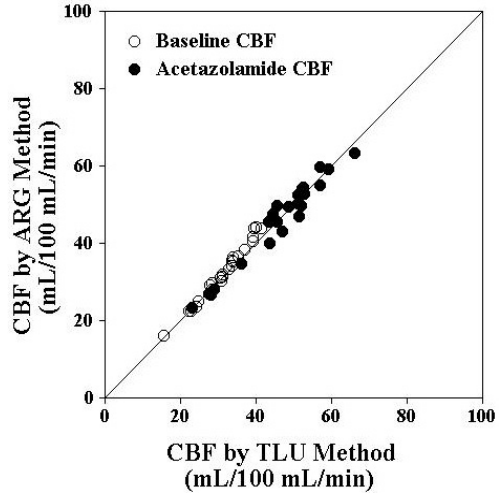

Fig. 3 Correlation between CBF_{TLU} and CBF_{ARG}.

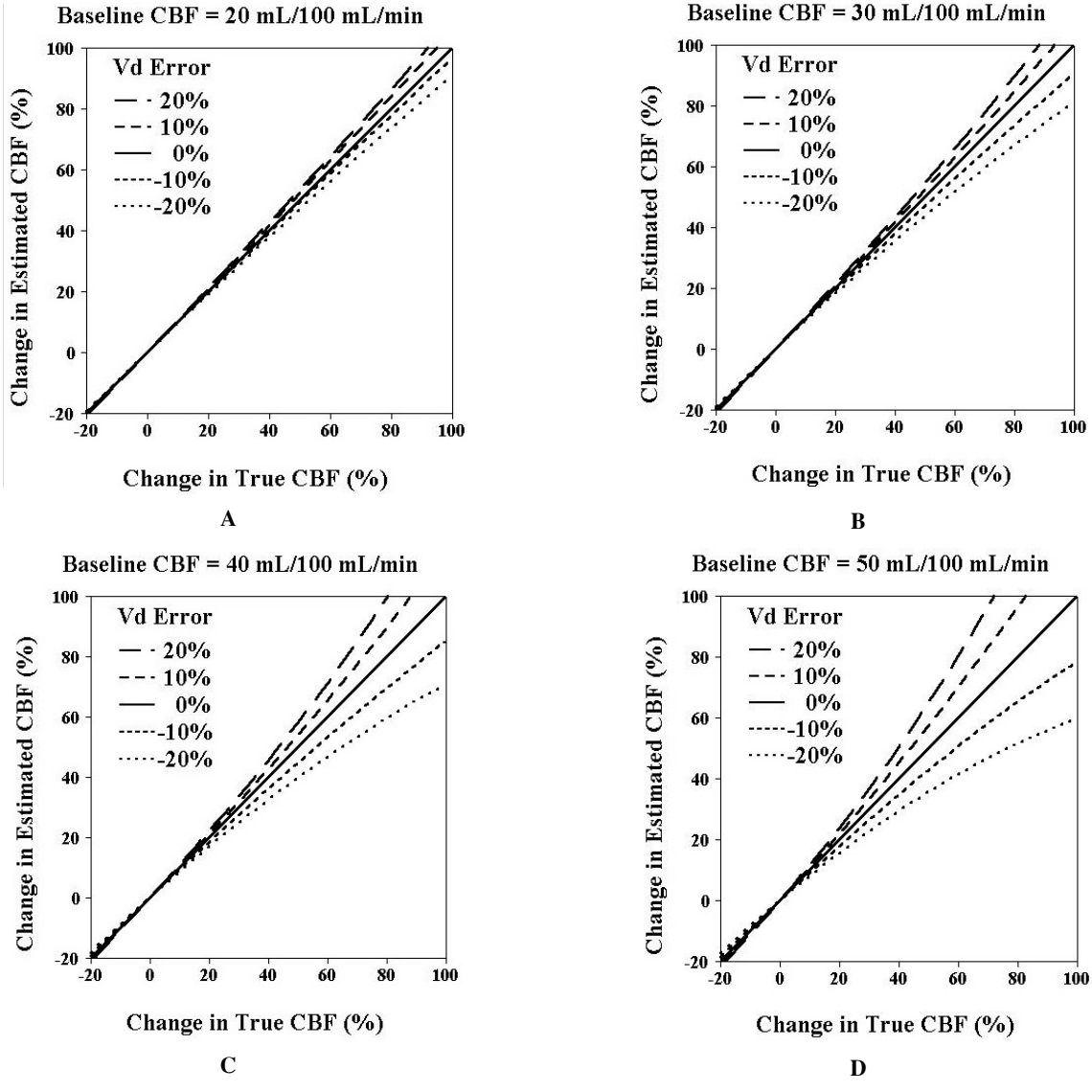

Fig. 4 Errors in changes in CBF in response to acetazolamide stress as calculated by ARG method with errors in V_d compared to assumed V_d.

DISCUSSION

CBF as calculated by the ARG method is dependent on an assumed V_d value.[8,9] Although the simulation study showed that errors in CBF calculated by the ARG method, resulting from errors in V_d, were larger when CBF was high, CBF_{ARG} was in good agreement with CBF_{TLU} for both the baseline and the acetazolamide stress studies. Previously, we reported that V_d value in the ARG method should be determined by the TLU method for each SPECT scanner system.[9] The present study showed that CBF values as calculated by the ARG method were consistent with CBF values as calculated by the TLU method, even in the acetazolamide stress study when the assumed V_d value in the ARG method was set to an average V_d value as calculated by the TLU method.

We have reported that regional differences in V_d of IMP in the living human brain are small, and that errors in CBF as calculated by the ARG method caused by regional differences in V_d are negligible.[17] In our investigation, V_d values in cerebrocortical regions ranged from 36 to 39 m*l*/m*l*. Because regional differences in V_d were small compared with the interindividual variation of V_d in the present study (38.7 ± 3.9 m*l*/m*l*, mean ± SD), errors in CBF in response to acetazolamide stress caused by regional differences in V_d would be expected to be small. However, regional differences in the vascular response to hypercapnia have been reported in humans.[18] Such regional differences may exist during acetazolamide stress, but further study will be required.

The simulation study showed that errors in changes in CBF in response to acetazolamide stress, those caused by

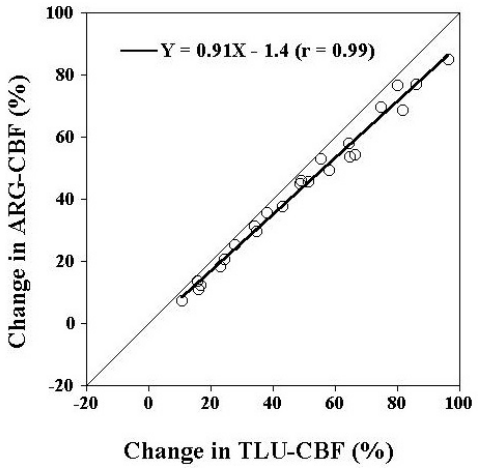

Fig. 5 Correlation between percent change in CBF_{TLU} and percent change in CBF_{ARG}.

errors in V_d compared to assumed V_d in the ARG method, were larger when the baseline CBF and changes in CBF were larger. However, the percent change in CBF_{ARG} was in good agreement with the percent change in CBF_{TLU}, indicating that errors in the CBF response to acetazolamide stress as calculated by the ARG method were negligible, even at high CBF responses. In the present study, the percent change in CBF_{ARG} was slightly less than the percent change in CBF_{TLU}. The simulation study showed that the degree of underestimation in changes in CBF due to errors in V_d was larger than that of overestimation in changes in CBF when the baseline CBF was 30 m*l*/100 m*l*/min. This might be one reason for the underestimation observed in the percent change in CBF_{ARG}. For measurement of CBF response to acetazolamide stress in major cerebral arterial occlusive disease, accuracy in the determination of lower ranges of CBF response is important.[6,7,11] In the present investigation, both simulation data and measured data showed that errors in changes in CBF in response to acetazolamide stress caused by errors in V_d were negligible when the change in CBF was small. In severe major cerebral arterial occlusive disease, a negative change in CBF in response to acetazolamide stress is often observed and is called the "steal phenomenon."[11] Although a negative change in CBF in the response to acetazolamide stress was not observed in patients in the present study, negligible errors in changes in CBF in the negative range were present in the simulation study.

V_d is an indicator of retention of IMP in the brain.[4] In the present study, it was assumed that V_d is not altered after intravenous infusion of acetazolamide. However, there are no reports concerning V_d of IMP in response to acetazolamide stress. The mechanism of cerebral vasodilatation in response to acetazolamide is not obvious. It has been reported that intravenous acetazolamide induces decreased pH in the brain.[19] However, the effects of cerebral acidosis on the retention of IMP in the brain are unknown. Because the CBF response to acetazolamide stress measured by IMP with the ARG method has been reported to be in good agreement with that measured by positron emission tomography with ^{15}O-labeled water,[11] the change in V_d in response to acetazolamide stress must be small.

In the ARG method, the arterial input function is determined by calibration of the standard input function with one-point arterial blood sampling. Therefore, if the shape of the arterial input function is changed greatly by acetazolamide stress, this might cause errors in CBF calculation. However, no significant effect of intravenous acetazolamide on the systemic circulation has been reported,[20] and no significant difference in arterial input function after intravenous infusion of IMP between baseline and acetazolamide stress studies has been reported.[21]

In conclusion, errors in the CBF response to acetazolamide stress as calculated by the ARG method, those caused by differences between true V_d and assumed V_d, were investigated. Although the simulation study showed that errors in changes in CBF in response to acetazolamide stress were larger when the baseline CBF and changes in CBF were larger, the percent change in CBF_{ARG} was in good agreement with the percent change in CBF_{TLU}. This indicates that errors in the CBF response to acetazolamide stress as calculated by the ARG method are negligible, even at high CBF responses. The ARG method is therefore reliable for the measurement of the CBF response to acetazolamide stress in major cerebral arterial occlusive disease.

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