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Regional differences in distribution volume of I-123 IMP in the human brain: Effect on CBF calculated by ARG method

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Objective: Two methods of quantitating cerebral blood flow (CBF) with iodine-123-labeled *N*-isopropyl-*p*-iodoamphetamine (I-123 IMP) and a two-compartment model had been proposed; one is the table look-up (TLU) method and the other is the autoradiographic (ARG) method. The TLU method provides values of the cerebral blood flow (CBF) values and distribution volume of I-123 IMP (Vd) independently. In the ARG method, a fixed Vd is applied for the entire brain to calculate CBF. Our purpose was to evaluate regional differences in Vd in the human brain, or possible effects of regional differences in Vd on CBF calculated by the ARG method. ***Methods:*** In the present study, two SPECT scans were acquired from each of eight normal subjects (aged 44.0 ± 16.7) at 40 min and 180 min of mid-scan-time after intravenous 1 min infusion of 111 MBq IMP. A single arterial blood sampling was performed 10 min after the IMP infusion. All images were anatomically normalized and analyzed with SPM99 and Matlab. We generated CBF and Vd images for each subject by the TLU method and evaluated differences in Vd among brain structures. We subsequently generated another set of CBF images by the ARG method and examined differences between CBF calculated by the TLU method and that by the ARG method. ***Results:*** Significant main effects of subject and brain structure in Vd were observed (two-way ANOVA). Vd values were higher in the deep gray matter than in the cerebral cortical regions. Among the cerebral cortical regions, no significant difference in Vd was observed. In spite of the significant differences in Vd among the brain structures, the voxel-by-voxel analyses as well as the ROI analyses revealed no statistically significant difference between CBF calculated by the TLU method and that by the ARG method. ***Conclusions:*** Although regional differences in Vd were observed, the present results support the assumption that a fixed Vd does not cause significant error in the calculation of CBF by the ARG method.

Key words: iodine-123 IMP, ARG, cerebral blood flow, anatomical standardization, distribution volume

INTRODUCTION

Iodine-123-labeled *N*-isopropyl-*p*-iodoamphetamine (I-123 IMP) is used as a cerebral blood flow (CBF) tracer in single photon emission computed tomography (SPECT).[1,2] Two methods that employ a two-compartment model had been proposed, one is the table look-up (TLU) method, which provides two functional parameters, namely, CBF and distribution volume of I-123 IMP (Vd) from two SPECT scans acquired at different time points,[3,4] and the other is the autoradiographic (ARG) method, which provides a quantitative CBF map from a single SPECT scan by means of a fixed Vd.[5,6] The latter method is theoretically equivalent to the former but more convenient in a clinical setting because it does not need a second scan that

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should be performed 180 min after the tracer infusion in the former method. On the other hand, the ARG method assumes a single fixed Vd for the entire brain.

There were few studies that quantitatively evaluated regional Vd in the human brain. Iida et al.[7] reported in their multicenter study that results from one institute did not show statistically significant differences in Vd among brain structures. On the other hand, we reported that Vd was not uniform in the brain, but we did not provide quantitative results.[8] Hatazawa et al.[9] also reported that there were statistically significant differences in Vd among brain structures; Vd in the basal ganglia was higher than those in the centrum semiovale and the entire brain. In these studies, it seems that the differences in Vd among brain structures were evaluated by using pooled data from different subjects and subject-specific regions-of-interest (ROIs), so that the differences in measured Vd among brain structures would be confounded by possible differences in subject-by-subject ROI settings and by intersubject differences in Vd.

It was shown that minor differences in Vd, particularly in regions where CBF is relatively low, such as in ischemic areas, would not cause a significant error in the calculation of CBF by the ARG method, theoretically and experimentally.[5,7,9] These results regarding Vd and calculated CBF, however, could also be confounded by differences in ROI settings and individual differences among subjects. In the case that there are indeed significant differences in Vd among the brain structures, ignoring these regional differences in Vd among brain structures would cause systematic error in calculated CBF.

The purpose of the present study was therefore to confirm whether there are differences in Vd among brain structures, by using an anatomical standardization technique, as well as to evaluate possible effects of the differences in Vd on CBF calculated by the ARG method and that by the TLU method with voxel-by-voxel analyses.

SUBJECTS AND METHODS

Subjects

SPECT was performed on eight normal volunteers (age 44.0 ± 16.7). None of them had any neurological or psychiatric disease, and informed consent was obtained from all subjects after proper explanation of the study being conducted, according to the Declaration of Human Rights of Helsinki 1975.

SPECT

Two SPECT scans were acquired, at 40 min (early image) and 180 min (delayed image) of mid-scan-time after intravenous infusion of 111 MBq IMP, lasting for 1 min. A SPECT scanner (SPECT 2000H; Hitachi Medico Corp., Tokyo, Japan),[10] equipped with a four-head rotating gamma camera, was used for scanning. It had an in plane resolution of 10 mm full width at half maximum (FWHM), and an axial resolution of 8 mm FWHM, and was fitted with low-energy, medium-resolution collimators. Image reconstruction was performed by filtered backprojection with a Butterworth filter (dimension 12, cutoff 0.125 cycle per pixel). Attenuation correction was carried out numerically by assuming the object shape to be an ellipse for each slice and the attenuation coefficient to be uniform (0.08/cm). Correction for scatter photons was not performed. Image slices were set up parallel to the orbitomeatal (OM) line and obtained at 8 mm intervals through the entire brain. One point arterial blood sampling from the brachial artery was performed 10 min after IMP infusion. Radioactivity of the whole blood was measured with a well counter and was used for calibration against the standard input function to obtain an arterial input function for the TLU method.[3,4] A cross-calibration scan was acquired with a cylindrical uniform phantom (20 cm in diameter and length) for calibration of the relative sensitivities of the SPECT scanner and the well counter system.

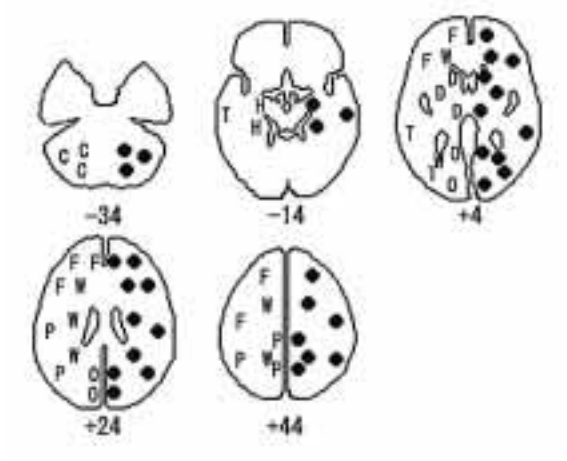

Fig. 1 Spherical ROIs are shown as circles in their maximum diameters on the right side of the contour of the mean CBF image. On the left side, arbitrary classifications of these ROIs into brain structures are shown; F: frontal cortex, P: parietal cortex, O: occipital cortex, T: temporal cortex, H: hippocampus, C: cerebellum, D: deep gray matter, W: white matter. Numbers indicate distance (in mm) from the AC-PC plane.

Data Analyses

We performed anatomical normalization and smoothing of images with statistical parametrical mapping software (SPM99, Wellcome Department of Cognitive Neurology, University College of London, London, UK)[11] implemented in MATLAB 5.3 (Mathworks, Sherborn, MA, USA). For each subject, first the linear and nonlinear parameters for anatomical normalization were estimated with the early image and a template image for SPECT.[12,13] Then both the early and delayed images were anatomically normalized with the above parameters after

coregistration of the delayed image with the early image. These anatomically normalized images were subsequently smoothed with an isotropic Gaussian kernel of 8 mm FWHM to compensate for possible minor coregistration error and individual differences in the gyrus anatomy. For each subject, a CBF image and a Vd image were generated from these images obtained by the TLU method. For the TLU method, the arterial input function was determined by calibrating the previously determined standard input function,[3,4] with the blood sample obtained at 10 min. A total of 34 spherical regions of interest (ROIs) (7 mm radius) were determined on both hemispheres, with reference to the mean anatomically standardized CBF image of the subjects and the standard T1-weighted MRI brain image of SPM99 (Fig. 1), and then superimposed onto each Vd image. Analyses for Vd values were performed with a commercial software package (Excel 2000, Microsoft, WA, USA). Vd values for homologous ROIs in both hemispheres of each subject were averaged. The mean Vd for the frontal, temporal, parietal and occipital cortices, hippocampus, deep gray matter (basal ganglia and thalamus), cerebellum and cerebral white matter (Fig. 1) was calculated by averaging Vd values for ROIs in each subject. Comparison of Vd values among these brain structures was performed with a two-way analysis of variance (two-way ANOVA; subject ∗ brain structure) without repeated measures, and post hoc Scheffe's test for multiple comparisons. After these analyses, another CBF image was calculated for each subject by the ARG method[5,6] assuming a fixed Vd of 40 m*l*/m*l* which is a clinical standard value for the ARG method. The differences between the CBF images calculated by the TLU method and those by the ARG methods were examined by a voxel-by-voxel paired t-test with SPM99.

Table 1 Summary of Vd and CBF values (mean ± standard deviation) calculated by the TLU method and those by the ARG method in brain structures for 8 normal subjects

	Vd (m*l*/m*l*)	TLU-CBF (m*l*/100 g/min)	ARG-CBF (ml/100 g/min)
Cerebellum	37.8 ± 9.8	35.6 ± 8.9	36.7 ± 11.5
Hippocampus	38.9 ± 10.0	27.6 ± 6.3	28.4 ± 7.7
Deep gray	40.3 ± 10.4	30.8 ± 6.4	32.2 ± 8.4
Frontal	36.8 ± 8.1	31.7 ± 5.6	32.2 ± 7.0
Parietal	37.3 ± 8.7	31.7 ± 5.7	32.3 ± 7.2
Temporal	39.0 ± 9.2	31.5 ± 7.0	32.8 ± 8.6
Occipital	36.1 ± 8.2	33.4 ± 7.4	33.8 ± 9.1
White matter	38.6 ± 11.2	22.1 ± 4.9	22.6 ± 5.7

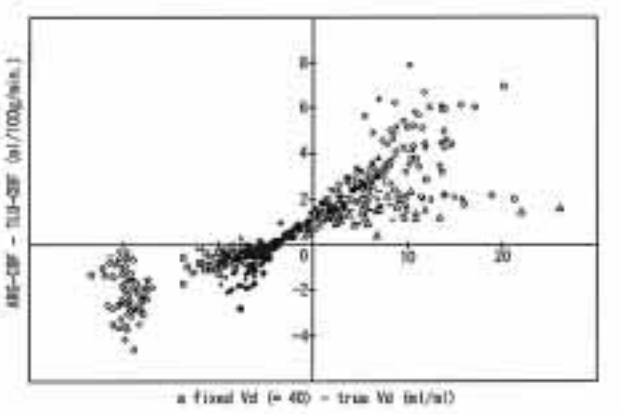

Fig. 2 Relationships between differences in fixed Vd (= 40) minus true Vd of each ROI (abscissa) and differences in CBF calculated by the ARG method minus that by the TLU method (ordinate). The same symbol indicates ROIs of the same subject.

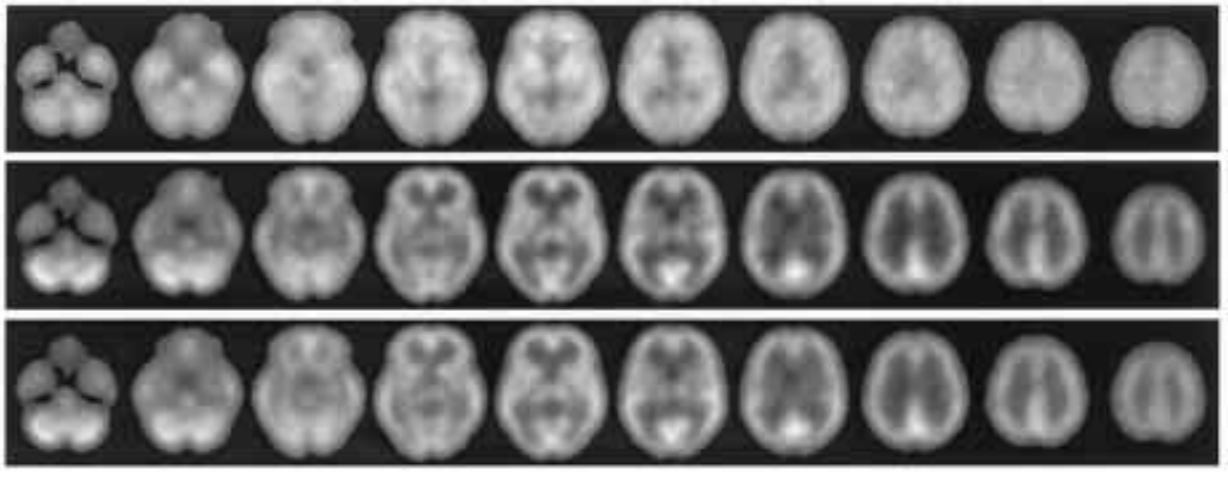

Fig. 3 Mean images of calculated Vd (*top*), CBF calculated by the TLU method (*middle*), and CBF calculated by the ARG method (*bottom*). Slices are oriented parallel to the AC-PC plane and shown every 10 mm starting at 34 mm below the AC-PC line. The left hemisphere of the brain is on the right and anterior on the top.

RESULTS

Table 1 summarizes Vd values in each brain structure. There were significant main effects of subject ($F(7,49) = 299.66$; $p < 0.0001$) and brain structure ($F(7,49) = 6.30$; $p < 0.0001$) on Vd values. The Vd in the deep gray matter was statistically significantly higher than that in the frontal, parietal and occipital cortices (Scheffe's test, $p < 0.05$). There was no other statistically significant difference between structures. The mean Vd for all ROIs was 37.9 ± 9.4 m*l*/m*l*. The differences between CBF calculated by the ARG method and that by the TLU method were plotted against the differences between a fixed Vd (= 40) and a true Vd calculated by the TLU method, for each ROI and subject (Fig. 2). The figure shows that the greater the difference between the true Vd and fixed Vd, the greater the error between CBF calculated by the TLU method and that by the ARG method, and the greater the variance among ROIs. Figure 3 shows the mean Vd images and CBF images calculated by the TLU method and those by the ARG method. Comparison of the two methods showed no statistically significant difference between TLU-CBF images and ARG-CBF images in voxel-by-voxel analyses (paired t-test, $p > 0.05$, uncorrected for multiple comparison for voxels). The CBF values calculated by the TLU method and those by the ARG method were averaged for the eight brain structures, in the same manner as in the analyses of Vd values, and are summarized in Table 1. There was also no statistically significant difference in CBF for the eight brain structures between TLU-CBF images and ARG-CBF images (paired t-test, $p > 0.05$, uncorrected for multiple comparison for structures).

DISCUSSION

In the present study, the differences in Vd values for I-123 IMP in brain structures of normal volunteers were evaluated by the anatomical standardization technique. The differences between CBF calculated by the TLU method and that by the ARG method were subsequently examined by voxel-by-voxel analyses as well as ROI analyses. There were significant differences in Vd values for I-123 IMP in brain structures. There was, however, no significant difference between the CBF calculated by the TLU method, in which CBF and Vd were calculated independently, and CBF calculated by the ARG method, in which CBF was calculated by using a fixed Vd value, not only in ROI analyses but also in voxel-by-voxel analyses.

Regional differences in distribution volume of I-123 IMP (Vd)

There were statistically significant differences in Vd values for I-123 IMP in the brain among subjects and brain structures. A recent study showed that Vd was independent of age and sex of subjects.[9] There would be, however, several other reasons for the significant intersubject differences in calculated Vd values, such as differences in the individual physiological state of the subjects when SPECT was performed, and minor technical fluctuations in the time of blood sampling. Because we did not intend to evaluate these subject-specific effects in the present study, we do not discuss the subject effect further.

There were few studies that reported regional differences in Vd in the human brain.[8,9] Hatazawa et al.[9] reported a higher Vd in the basal ganglia than that in the centrum semiovale, which is also higher than the mean Vd in the entire brain. In the present study, we found that the Vd in the deep gray matter was higher than that in the cerebral cortical areas, but the Vd in the deep white matter was not statistically significantly lower than that in other structures. There was, on the other hand, a report that showed no statistically significant difference in Vd in the brain, but it seems that intersubject difference was not taken into account, so that the difference in Vd would not be detected as statistically significant because of the possible large variance due to intersubject difference (Table 4 of Iida et al.).[7] One reason for the differences in Vd in the brain might be the nonuniformity of the physiological brain-blood partition coefficient of IMP. But there were animal studies that showed IMP binding to high-capacity, relatively homogeneously distributed amine-binding sites in the brain,[1] and that IMP "redistribution" in ischemic areas depends on blood flow rather than on physiological brain function.[14] Another possibility is that the fraction of the brain tissue mass per given ROI would differ among ROIs. Using normal subjects, ROIs in the deep gray matter and white matter would likely consist of comparatively homogeneous structures, but ROIs, or voxels, in the cerebral cortex would inevitably consist of inhomogeneous structures, including the gray matter, white matter, and cerebrospinal fluid space. Iida et al.[15] showed in their $H_2{}^{15}O$ PET CBF study that CBF in the cerebral cortical ROI could be substantially underestimated in the absence of partial volume correction. It could be possible that Vd for a cerebral cortical ROI in the present study was also underestimated due to the partial volume effect, particularly with the inclusion of the cerebrospinal space. There were studies, on the other hand, that reported a method for calculating CBF and the partition coefficient of IMP,[16] which is practically equivalent to Vd, and use these values for differential diagnosis of Parkinsonisms.[17] Further studies would be necessary to evaluate the clinical significance of Vd images in degenerative brain diseases, taking into consideration for changes in brain tissue fraction, such as regional brain atrophy.

Differences in calculated CBF

Although significant differences in Vd values were observed among different brain structures, CBF values

calculated by the ARG method with a fixed Vd throughout the whole brain were not significantly different from those by the TLU method. The results were consistent with previous studies.[5,7] The results hold regardless of the brain region, that is, the cortical, subcortical gray matter and white matter, in normal subjects. The CBF values in the present study were considerably lower than those obtained with other methods,[18–20] but were equivalent to the normal value obtained with the IMP-ARG method.[9] The difference between CBF values calculated by the two methods depends on the difference between a fixed Vd and true Vd, in line with a theoretical study.[5] There was also a significant subject effect on Vd difference (described above), so that errors tend to be larger in some subjects but not in others (Fig. 2). These results suggest that although CBF for a subject calculated by the ARG method might differ from that calculated by the TLU method, there is no significant difference between the mean CBF values obtained by the two for many subjects, unless a fixed Vd is noticeably different from the mean true Vd. Theoretically, it is also expected that the error sensitivity of CBF to Vd in brain structures where CBF is relatively low, is small.[5] Although the present results might suggest that CBF in the gray matter is not high enough to result in a significant error in CBF calculated by assuming a fixed Vd, there is a study that showed less accurate results in using the ARG method for a high CBF state caused by an acetazolamide challenge,[21] but this issue remains to be studied further.

CONCLUSION

We evaluated differences in Vd of I-123 IMP in brain structures of normal subjects by using the anatomical normalization technique, and found a higher Vd for the deep gray matter than in the cerebral cortical regions. In spite of the significant differences in Vd in the brain structures, the voxel-by-voxel analyses as well as the ROI analyses revealed no statistically significant difference between CBF calculated by the TLU method and that by the ARG method. This study showed that the assumption of a fixed Vd in the calculation of CBF by the ARG method did not cause a significant error compared with the TLU method in a group analysis.

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