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·Original Article·

CBF/CBV maps in normal volunteers studied with ^{15}O PET: a possible index of cerebral perfusion pressure

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ABSTRACT

Local cerebral perfusion pressure (CPP) is a primary factor controlling cerebral circulation and previous studies have indicated that the ratio of cerebral blood flow (CBF) to cerebral blood volume (CBV) can be used as an index of the local CPP. In this study, we investigated whether the CBF/CBV ratio differs among different brain structures under physiological conditions, by means of ^{15}O positron emission tomography. Nine healthy volunteers (5 men and 4 women; mean age, 47.0 ± 1.2 years) were studied by $H_2{}^{15}O$ bolus injection for CBF measurement and by $C^{15}O$ inhalation for CBV measurement. The CBF/CBV ratio maps were created by dividing the CBF images by the CBV images after anatomical normalization. Regions of interest were placed on the CBF/CBV maps and comparing the regions. The mean CBF/CBV ratio was highest in the cerebellum (19.3 ± 5.2/min), followed by the putamen (18.2 ± 3.9), pons (16.4 ± 4.6), thalamus (14.5 ± 3.3), cerebral cortices (13.2 ± 2.4), and centrum semiovale (11.5 ± 2.1). The cerebellum and putamen showed significantly higher CBF/CBV ratios than the cerebral cortices and centrum semiovale. We created maps of the CBF/CBV ratio in normal volunteers and demonstrated higher CBF/CBV ratios in the cerebellum and putamen than in the cerebral cortices and deep cerebral white matter. The CBF/CBV may reflect the local CPP and should be studied in hemodynamically compromised patients and in patients with risk factors for small-artery diseases of the brain.

Keywords: cerebral perfusion pressure; cerebral blood flow; cerebral blood volume; $H_2{}^{15}O$; $C^{15}O$

INTRODUCTION

Cerebral perfusion pressure (CPP) is one of the essential factors in maintaining the cerebral circulation. Powers and Derdeyn *et al*. proposed a staging method for cerebral hemodynamic crises based on the CPP, cerebral blood flow (CBF), cerebral blood volume (CBV), and oxygen extraction fraction (OEF)[1,2]. However, the regional CPP in the brain could not be non-invasively measured in humans.

Based on clinical observations, the local CBF/CBV ratio can be used as an index of the local CPP[3,4]. Schumann *et al*. evaluated the CBF/CBV ratio during global CPP manipulation by varying the mean arterial blood pressure (MABP) in anesthetized baboons[5] and demonstrated that the CBF/CBV ratio is significantly correlated with the MABP in the range where the cerebral metabolic rate of oxygen is maintained. As the CPP is defined as MABP minus intracranial pressure, the cortical CBF/CBV ratio could be an index of the local CPP in the brain.

In the present study, we created CBF/CBV ratio maps in normal volunteers by means of ^{15}O PET, and examined the possible existence of differences in the CBF/CBV ratio maps among different brain regions under physiological conditions.

PARTICIPANTS AND METHODS

Normal Volunteers

^{15}O PET studies were performed in nine normal volunteers (4 men and 5 women; mean age ± SD = 50.9 ± 0.4 years). The criteria for defining "normality" were as follows: (1) no past history of neurological and psychiatric disorders, heart failure, liver and renal dysfunction, respiratory diseases, acute inflammatory disease, autoimmune diseases, or cancer, (2) no smoking or alcohol habit, (3) no significant abnormality on MR imaging or MR angiography of the brain, and (4) no history of medication within the previous 3 months. This study was conducted with the approval of the Ethics Committee of Osaka University Hospital. Written informed consent was given by all participants.

PET Measurements

The PET images were obtained in the 3-D mode using a SET-3000 GCT/X scanner (Shimadzu Corp., Kyoto, Japan), the performance of which has been described[6]. Briefly, the intrinsic spatial resolution was 3.5-mm full-width at half maximum (FWHM) in-plane and 4.2-mm FWHM axially. Transmission scanning with an external point source (^{137}Cs) was performed for attenuation correction. The PET images were reconstructed by a filtered-back projection method after 3D Gaussian smoothing with a 6-mm FWHM. Scatter events were corrected by the hybrid dual-energy window method combined with a convolution-subtraction method[6]. Participants were studied under room light and minimal mechanical noise, with their eyes closed and ears unplugged. The head of each participant was immobilized by a belt to minimize any motion during the study and between the CBV and CBF measurements.

A cannula was inserted into the radial artery for measuring the arterial input function. For the CBV study, the participants continuously inhaled $C^{15}O$ gas (3.0 GBq/min) for 1 min. Static 4-min scanning was started 3 min after the completion of $C^{15}O$ inhalation[7]. Arterial blood was collected 3 times during the scanning period to measure the whole-blood radioactivity. In the equation, the small-to-large vessel hematocrit ratio was fixed at 0.85[8].

The CBF study was performed more than 10 min after completion of the $C^{15}O$ study to minimize any residual ^{15}O activity. For the CBF study, a bolus of 370 MBq $H_2{}^{15}O$ was injected intravenously, and simultaneously a 3-D list-mode data acquisition over a period of 180 s was started[9,10]. Continuous arterial blood sampling was performed using a β-detector system to determine the whole-arterial blood radioactivity. Delay and dispersion occurring in the β-detector system were corrected by methods described previously[11]. Quantitative measurement of the CBF and CBV by the 3-D mode PET scanner has been validated[6].

Partial arterial O_2 pressure (PaO_2), partial arterial CO_2 pressure ($PaCO_2$), pH, hematocrit (Ht), and hemoglobin concentration (Hb) were monitored continuously during the study. The systemic blood pressure and heart rate were also monitored during the PET study. MABP was calculated as: [diastolic BP + (systolic BP − diastolic BP) / 3].

Data Analysis

The CBF images were transformed to the standard brain size and shape of a built-in PET template, using SPM8 software (Wellcome Department of Imaging Neuroscience: http://www.fil.ion.ucl.ac.uk/spm/). Parametric maps of CBV were created using the same parameters as those for CBF normalization. The resultant images had the same anatomic format, with an isotropic voxel size of 2 mm. The CBF/CBV images were created by dividing the normalized CBF images by the normalized CBV images after smoothing (FWHM = 8 mm). PET/MRI fusion images were created with a normalized template of T1-weighted MRI using Osirix software (32-bit, version 3.8.1). Regions of interest (ROIs) were drawn on the normalized CBF, CBV, and CBF/CBV images. Circular ROIs were placed on 3 sequential cross-sections of the pons and thalamus (16 mm in diameter), and elliptical ROIs (16 × 32 mm) were placed on 3 sequential cross-sections in each of the cerebellum (cerebellar hemisphere), putamen, centrum semiovale, and cerebral cortices (frontal, temporal, occipital, and parietal). All the ROIs were manually set apart from the superior and inferior sagittal sinuses, straight sinus, transverse sinus, sigmoid sinus, cavernous sinus, basilar venous plexus, superior and inferior petrosal sinuses, and large cerebral veins, such as great vein of Galen, internal cerebral vein, and basal vein of Rosenthal. Regional differences in the CBF/CBV ratio were compared by the paired *t* test. Probability values <0.05 determined by Bonferroni's correction for multiple comparisons were considered to denote statistical significance.

RESULTS

There were no significant differences in the physiological parameters between the CBV and CBF measurement periods (Table 1). The mean CBF, CBV and CBF/CBV ratio for each brain region are shown in Table 2. The cerebellum showed the highest CBF/CBV ratio, while the cerebral deep white matter (centrum semiovale) showed the lowest ratio. The mean CBF/CBV ratios in the cerebellum and putamen were higher than those in the cerebral cortices or centrum semiovale (P <0.006). The normalized sum images for CBF, CBV, and CBF/CBV ratio, along with fusion images of CBF/CBV and MRI T1-weighted images are shown in Figure 1. Among the regions of the cerebral cortex, the frontal cortex showed the highest CBF/CBV ratio, followed by the temporal, parietal, and occipital cortex. The CBF/CBV ratio in the frontal cortex was higher than that in the occipital cortex (P <0.006).

Table 1. Arterial blood gas parameters and blood pressure in $C^{15}O$ and $H_2{}^{15}O$ studies

	$C^{15}O$ study	$H_2{}^{15}O$ study	P value
pH	7.403 ± 0.021	7.401 ± 0.015	0.66
PaO_2 (mmHg)	85.6 ± 8.3	83.2 ± 8.8	0.16
$PaCO_2$ (mmHg)	39.8 ± 5.0	40.0 ± 4.1	0.71
MABP (mmHg)	95.0 ± 11.5	93.4 ± 9.9	0.17
Hb (g/dl)	12.5 ± 1.6		
Ht (%)	38.4 ± 4.7		

Mean ± SD; paired *t*-test.

DISCUSSION

In the present study, we created anatomically normalized CBF/CBV ratio maps in normal volunteers based on ^{15}O PET, and demonstrated that the CBF/CBV ratio was not uniformly distributed in the brain. The cerebellum, putamen, thalamus, and brainstem (pons) showed relatively higher CBF/CBV ratios than the cerebral cortex and deep white matter (centrum semiovale) under physiological conditions.

The CBF/CBV ratios determined here are consistent with the calculated values from previous ^{15}O PET studies. The regional distribution of the mean transit time (MTT; inverse of the CBF/CBV ratio) in normal young volunteers has been investigated in previous studies. Ibaraki *et al*. studied the distribution of the MTT in seven healthy volunteers (aged 20 to 21 years) based on ^{15}O-PET ($H_2{}^{15}O$ and $C^{15}O$)[12]. Regional differences were observed,

Table 2. CBF, CBV, and CBF/CBV ratio for each brain region

	CBF (mL/100 mL/min)	CBV (mL/100 mL)	CBF/CBV (/min)
Cerebellum	44.3 ± 7.2	2.52 ± 0.40	19.3 ± 5.2
		(2.21 ± 0.35)*	(22.0 ± 5.9)*
Putamen	46.3 ± 5.7	2.62 ± 0.41	18.2 ± 3.9
		(2.42 ± 0.38)*	(19.7 ± 4.2)*
Pons	42.1 ± 6.0	2.74 ± 0.69	16.4 ± 4.6
Thalamus	45.2 ± 6.9	3.12 ± 0.51	14.5 ± 3.3[b]
Frontal cortex	38.6 ± 6.6	2.70 ± 0.32	14.4 ± 2.4[a,b]
Temporal cortex	43.1 ± 5.7	3.23 ± 0.22	13.3 ± 2.5[a,b]
Parietal cortex	35.2 ± 4.9	2.65 ± 0.25	13.2 ±1.9[a,b]
Occipital cortex	39.3 ± 5.6	3.23 ± 0.52	12.1 ± 2.4[a,b,d,e]
Centrum semiovale	21.3 ± 2.7	1.78 ± 0.22	11.5 ± 2.1[a,b,c]

*A small-to-large hematocrit ratio of 0.92 was used for the putamen and 0.97 for the cerebellum in the CBV calculation. P <0.05 *versus* [a]cerebellum, [b]putamen, [c]pons, [d]thalamus, and [e]frontal cortex (adjusted for multiple comparisons); mean ± SD.

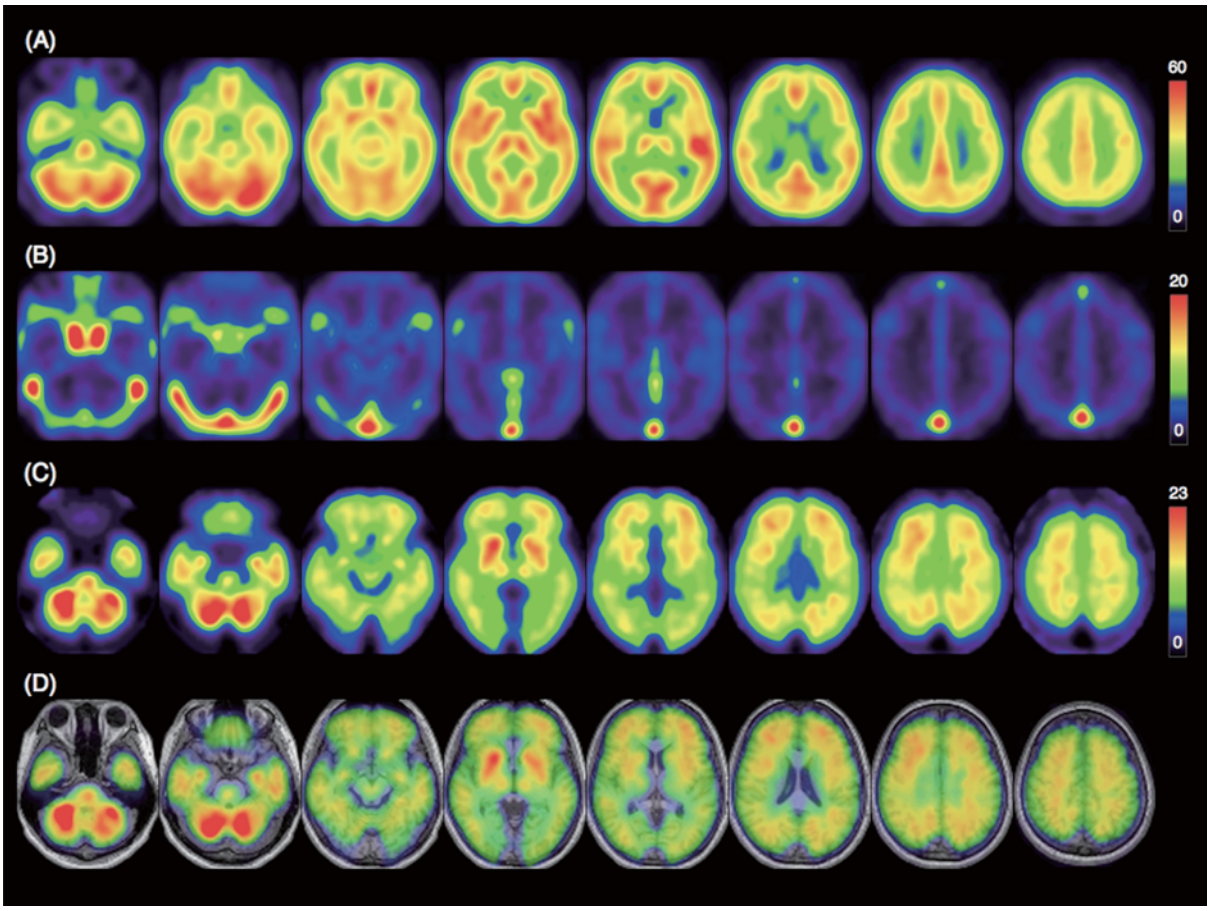

Fig. 1. Average PET images of (A) CBF, (B) CBV, and (C) CBF/CBV ratio with (D) PET/MRI fusion images of CBF/CBV ratio.

the MTTs being shorter in the order thalamus, putamen, cerebellum, cerebral cortex, and centrum semiovale. Ito *et al.* (2003) reported that in young male volunteers (19–27 years of age), the MTT was significantly shorter in the cerebellum, thalamus, and putamen than in all the neocortical regions, and significantly longer in the centrum semiovale than in almost all other regions[13]. Our results from middle-aged volunteers are consistent with the above findings. The mean CBF/CBV ratio in the temporal cortex was 13.3 in the present study, 15.4 in the study reported by Ibaraki *et al.* and 16.7 in the report by Ito *et al.*[12,13]. The lower mean CBF/CBV ratio in this study is considered to result from an age-related decline in the CBF and no change in the CBV[14].

In the CBV measurement by $C^{15}O$ inhalation, the regional CBV was estimated under the assumption of a constant small-to-large vessel hematocrit ratio (0.85) among brain structures[8]. If the hemodilution in the small vessels were to differ among regions, correct estimation of the regional CBV and CBF/CBV ratio may be difficult. Okazawa *et al.* measured the regional red blood cell volume and plasma volume separately by means of $C^{15}O$ and ^{62}Cu-human serum albmin-dithiosemicarbazone PET[15]. In their study, the small-to-large vessel hematocrit ratios in the cortical gray matter, white matter, and basal ganglia of normal volunteers were 0.85 ± 0.07, 0.86 ± 0.07 and 0.92 ± 0.04, respectively. Yamauchi *et al.*, by means of a similar combined PET study, reported that the cerebellar small-to-large hematocrit ratio was ~0.97[16]. When we applied a ratio of 0.92 for the putamen and 0.97 for the cerebellum instead of 0.85 in the CBV calculation, the CBF/CBV ratio increased by 8% for the putamen and by 14% for the cerebellum, further enhancing the regional differences in the CBF/CBV ratio between the cerebellum/basal ganglia

and cerebral cortices/centrum semiovale. Cremer *et al.* reported relatively constant tissue hematocrit values (%) in rats: 31.01 ± 0.61 for the caudate/putamen, 28.66 ± 0.66 for the thalamus, 30.80 ± 0.55 for the cerebellum, and 30.34 ± 0.49 (auditory cortex) to 32.05 ± 0.83 (visual cortex) for the cerebral cortices[17]. Based on these reports, we considered that the CBF/CBV ratios in the cerebellum and putamen were higher than those in the cerebral cortex and centrum semiovale.

Schumann *et al.* have demonstrated a linear correlation between the cortical CBF/CBV ratio and the MAP, and claimed that the cortical CBF/CBV ratio could be used as an index of the cortical CPP[5]. However, it was still unknown whether the CBF/CBV ratios in the basal ganglia and cerebellum respond to changes of the MABP as found in the cortical regions. In their study, the CBF/CBV ratio maps of baboons showed proportional changes in the cerebral cortex and putamen/thalamus during hypotension and hypertension. Based on these findings, we speculated that the CBF/CBV ratio maps may reflect the local CPP not only in the cerebral cortices, but in the whole brain. We further speculate that the CPP in the cerebellum, putamen, thalamus, and brainstem may be higher than that in the cerebral cortices and deep white matter.

What are the clinical implications of the findings of the present study? Brain regions showing high CBF/CBV ratios (putamen, thalamus, pons, and cerebellum) are vulnerable to small-artery diseases. Kinoshita *et al.* reported that in hypertensive stroke patients, brain microbleeds were found by MRI in the lentiform nucleus (47%), thalamus (42%), brainstem (34%), and cerebellum (25%)[18]. Lacunar infarction was associated with a similar finding of microbleeds. Kato *et al.* reported a high incidence of microbleeds in the subcortical white matter, thalamus, basal ganglia, brainstem (predominantly in the pons), and cerebellum[19]. Further analysis of CBF/CBV ratio maps and the local CPP values may reveal the probability of microangiopathy and the mechanisms of formation of microbleeds/lacunar infarcts in hypertensive patients. In patients with steno-occlusive arterial diseases, the CBF/CBV ratio maps would reveal the extent and magnitude of the CPP decline, as proposed by Gibbs *et al.*, Sette *et al.*, and Schumann *et al.*[3-5].

In the clinical setting, it is much easier to measure the CBF and CBV by means of SPECT than by ^{15}O PET. Several SPECT tracers are available for CBF and for CBV (^{99m}Tc-human serum albumin) imaging. By combining CBF measurements with CBV SPECT, CBF/CBV ratio maps can be prepared for each patient. In ^{15}O PET studies, we can obtain quantitative images with higher spatial resolution than in SPECT. The CBF/CBV ratio of a small region can be accurately evaluated by ^{15}O PET.

CONCLUSIONS

In this study we demonstrated, based on the CBF/CBV ratio maps of healthy volunteers, the normal distribution of the local CPP in the brain. The cerebellum and putamen, which are common sites of hypertensive intracerebral hemorrhage, showed higher CBF/CBV ratios than the cerebral cortices and deep white matter under normal physiological conditions. CBF/CBV maps should be studied in further detail in hemodynamically compromised patients and in patients with risk factors for small-artery diseases of the brain.

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