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Arterial fraction of cerebral blood volume in humans measured by positron emission tomography

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In quantitative functional neuroimaging with positron emission tomography (PET) and magnetic resonance imaging (MRI), cerebral blood volume (CBV) and its three components, arterial, capillary, and venous blood volumes are important factors. The arterial fraction for systemic circulation of the whole body has been reported to be 20–30%, but there is no report of this fraction in the brain. In the present study, we estimated the arterial fraction of CBV with PET in the living human brain. $C^{15}O$ and dynamic $H_2{}^{15}O$ PET studies were performed in each of seven healthy subjects to determine the CBV and arterial blood volume (V_a), respectively. A two-compartment model (influx: K_1, efflux: k_2) that takes V_a into account was applied to describe the regional time-activity curve of dynamic $H_2{}^{15}O$ PET. K_1, k_2 and V_a were calculated by a non-linear least squares fitting procedure. The V_a and CBV values were 0.011 ± 0.004 m*l*/m*l* and 0.031 ± 0.003 m*l*/m*l* (mean ± SD), respectively, for cerebral cortices. The arterial fraction of CBV was 37%. Considering the limited first-pass extraction fraction of $H_2{}^{15}O$, the true arterial fraction of CBV is estimated to be about 30%. The estimated arterial fraction of CBV was quite similar to that of the systemic circulation, whereas it was greater than that (16%) widely used for the measurement of cerebral metabolic rate of oxygen ($CMRO_2$) using PET. The venous plus capillary fraction of CBV was 63–70% which is a important factor for the measurement of $CMRO_2$ with MRI.

Key words: cerebral blood volume, artery, vein, human, brain, PET

INTRODUCTION

Quantitative functional neuroimaging with positron emission tomography (PET) and magnetic resonance imaging (MRI) has been widely used to investigate the neurophysiology and the pathophysiology of cerebrovascular and neuropsychiatric diseases. For such quantitative imaging, cerebral blood volume (CBV) is an important factor. The CBV in a brain region is the sum of three components, i.e., the arterial, capillary, and venous blood volumes.[1–3] The fractions of these component are needed for quantitative functional imaging with PET and MRI, but there has been no report of these fractions in the brain.

Since regional intravascular radioactivity in the brain contributes to the regional radioactivity measured by PET,[4] the correction of intravascular radioactivity is needed in quantitative PET analysis.[1] The CBV can be measured by ^{15}O-labeled carbon monoxide ($C^{15}O$) and PET.[5] Nevertheless when a tracer that has a relatively high first-pass extraction fraction is used, the radioactivity concentration in the arterial blood differs from that in the capillary and venous blood.[3] For such tracers, determination of the arterial fraction of CBV is necessary for correction of intravascular radioactivity.[2]

Whereas the blood oxygenation level dependent (BOLD) contrast measured by functional magnetic resonance imaging (fMRI) has been used as an indicator of neuronal activity,[6] the measurement of the cerebral metabolic rate of oxygen ($CMRO_2$) by means of BOLD contrast has recently been reported.[7] Since the concentration

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of oxygenated blood in venous and capillary blood is the main contributor to BOLD contrast,[6,8] the venous plus capillary fraction of CBV is an important factor for the measurement of $CMRO_2$ by means of BOLD contrast with fMRI.[7–9]

^{15}O-labeled water ($H_2{}^{15}O$) is a tracer that can freely diffuse through the blood-brain barrier. After intravenous infusion of $H_2{}^{15}O$, the radioactivity concentration in the capillary and venous blood is same as that in the brain tissue,[10] but it differs from that in the arterial blood. The radioactivity concentration in the arterial blood can be differentiated on a regional time-activity curve by kinetic analysis with a two-compartment model that takes into account the contribution of radioactivity from the arterial blood in a region of interest. Such a two-compartment model has been used to calculate the blood flow and arterial blood volume in myocardium using $H_2{}^{15}O$.[11] Recently this two-compartment model has been applied to describe the regional time-activity curve of $H_2{}^{15}O$ in the brain.[3] With this model, the arterial blood volume in a brain region can be calculated from dynamic $H_2{}^{15}O$ PET data.

In the present study we estimated the arterial fraction of CBV by means of PET in the living human brain. Both $C^{15}O$ and $H_2{}^{15}O$ PET studies were performed in each of seven healthy subjects. The CBV and arterial blood volume were determined from $C^{15}O$ and $H_2{}^{15}O$ PET studies, respectively.

MATERIALS AND METHODS

Theory

The CBV (ml/ml) in a brain region is assumed to be the sum of the three components as follows.[1–3]

$$CBV = V_a + V_c + V_v \qquad \text{(Eq. 1)}$$

where V_a is the arterial blood volume (ml/ml), V_c is the capillary blood volume (ml/ml), V_v is the venous blood volume (ml/ml).

To describe the kinetics of $H_2{}^{15}O$ in the brain, the two-compartment model that takes V_a into account (V_a model, Fig. 1) is used. According to this model, the radioactivity concentration in a brain region can be expressed as follows.[3,11]

$$C_b(t) = K_1 \cdot C_a(t) \otimes e^{-k_2 \cdot t} + V_a \cdot C_a(t) \qquad \text{(Eq. 2)}$$

where $C_b(t)$ is the radioactivity concentration in a brain region, $C_a(t)$ is the radioactivity concentration in the arterial whole blood (arterial input function), K_1 is the influx rate constant (ml/ml/min) and k_2 is the efflux rate constant (min^{-1}). The influx rate constant K_1 corresponds to the cerebral blood flow (CBF). The K_1/k_2 ratio is defined as the distribution volume (V_d, ml/ml).

Subjects

The study was approved by the Ethics Committees of Akita Research Institute of Brain and Blood Vessels. Seven healthy volunteers including 4 men and 3 women (age range, 22–61 yr; average, 49.1 yr) were recruited and gave written informed consent. The subjects were determined to be healthy based on their medical history, physical examination, blood screening analysis and MRI of the brain.

PET procedure

The PET system used was Headtome V (Shimadzu Corp., Kyoto, Japan)[12] which provides 47 sections with a center to center distance of 3.125 mm. The intrinsic spatial resolution was 4.0 mm full width at half maximum (FWHM) in-plane and 4.3 mm FWHM axially. With a Butterworth filter, the reconstructed in-plane resolution was approximately 8 mm FWHM.

$C^{15}O$ study

To measure the CBV, a $C^{15}O$ PET study was performed.[5] The static PET scan was started 3 minutes after 1 minute of continuous inhalation of $C^{15}O$ gas (approximately 5 GBq by mouth). The scan time was 4 minutes. Three arterial blood samples were taken during PET scanning. The transmission scanning for attenuation correction was performed just before $C^{15}O$ PET scanning.

$H_2{}^{15}O$ study

After the $C^{15}O$ PET study, 360-second dynamic scanning was performed following continuous intravenous infusion of $H_2{}^{15}O$ over 2 minutes. The scan sequence consisted of six 5-sec frames, six 15-sec frames and eight 30-sec frames. The dose of radioactivity was 1.1 to 1.4 GBq at the start of the scanning. The arterial input function was obtained by continuous measurement of arterial whole blood radioactivity with a beta probe. Dispersion and delay occurring in the beta detector system and in the internal-arterial line were corrected according to the methods previously reported.[13,14] The dispersion was corrected by deconvolution with a single exponential function assuming the dispersion time constant to be 4 sec. The delay was corrected by means of a non-linear curve fitting to the time-activity data of the whole brain (gantry coincidence curve of PET scanner) with a single-tissue compartment model that takes the delay into account. Two blood samples were taken at the beginning and at the end of scanning to measure the arterial CO_2 gaseous pressure. A head fixation system with individual molds for each subject was used to minimize head movement over the period of the PET measurements.

Regions of interest

Regions of interest (ROIs) were drawn on the PET images. ROIs were defined for four neocortical regions representing the frontal, temporal, parietal, and occipital lobe. The ROIs were elliptical in shape with a short axis of 16 mm and long axis of 32 mm. Each ROI was drawn

in three adjacent sections, and data were pooled to obtain the average radioactivity concentration for the whole volume of interest. To obtain regional time-activity curves, regional radioactivity was calculated for each frame, corrected for decay and plotted against the time.

Kinetic analysis

The two-compartment model that takes V_a into account (V_a model, Fig. 1) was used to describe the $H_2{}^{15}O$ time-activity curves for each region. The rate constants and V_a were estimated by non-linear curve fitting to the regional time-activity curves in a least-squares manner.[15] The model equation solved in the convolution integral procedure (Eq. 2) was used for this analysis. The two-compartment model assuming V_a to be zero (NoV_a model) which has widely been used to calculate CBF[16,17] was also used

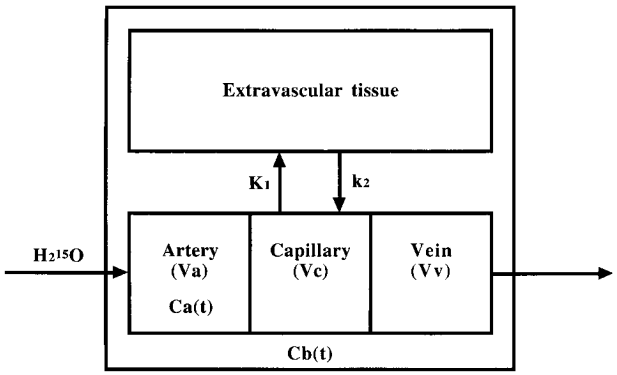

Fig. 1 Two-compartment model taking V_a into account (V_a model) to describe the kinetics of $H_2{}^{15}O$ in the brain.

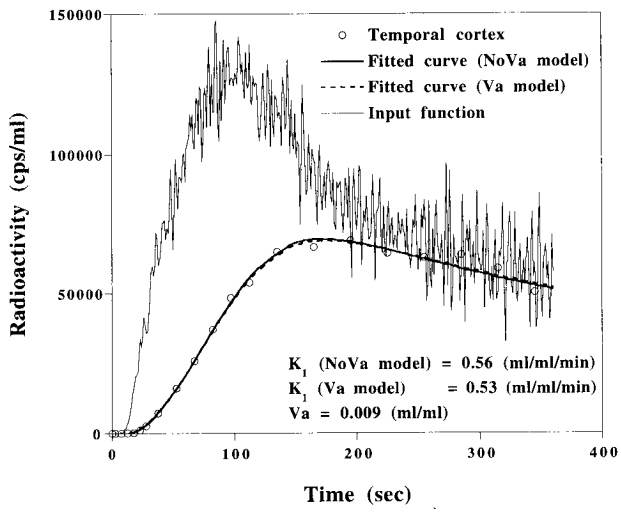

Fig. 2 Typical time-activity data for a cerebral cortical region and fitted curves in both the V_a and NoV_a model.

Table 1 The K_1, V_d and Akaike information criterion (AIC) values obtained by kinetic analyses for $H_2{}^{15}O$ PET

Region	NoV_a model			V_a model			
	K_1 (ml/ml/min)	V_d (ml/ml)	AIC	K_1 (ml/ml/min)	V_d (ml/ml)	AIC	V_a (ml/ml)
Frontal cortex	0.47 ± 0.10‡	0.74 ± 0.06	334 ± 12†	0.45 ± 0.10	0.74 ± 0.05	327 ± 8	0.009 ± 0.005
Temporal cortex	0.52 ± 0.06†	0.76 ± 0.06	341 ± 8†	0.48 ± 0.08	0.76 ± 0.05	333 ± 8	0.013 ± 0.007
Occipital cortex	0.51 ± 0.06†	0.74 ± 0.05	345 ± 12†	0.49 ± 0.06	0.74 ± 0.05	337 ± 13	0.009 ± 0.004
Parietal cortex	0.49 ± 0.08†	0.75 ± 0.03	338 ± 14‡	0.45 ± 0.09	0.75 ± 0.03	329 ± 12	0.014 ± 0.006
Cerebral cortices*	0.50 ± 0.07†	0.75 ± 0.04	340 ± 9†	0.47 ± 0.08	0.75 ± 0.03	332 ± 8	0.011 ± 0.004

Values are mean ± SD

*Average of frontal, temporal, occipital and parietal cortices

Significant difference in comparison to the V_a model (paired t-test): †$p < 0.01$, ‡$p < 0.05$

Table 2 The CBV, V_a, $V_v + V_c$ (= CBV − V_a) and arterial and venous plus capillary fraction of CBV (V_a/CBV, $V_v + V_c$/CBV)

Region	CBV (ml/ml)	V_a (ml/ml)	$V_v + V_c$ (ml/ml)	V_a/CBV	$(V_v + V_c)$/CBV
Frontal cortex	0.025 ± 0.004	0.009 ± 0.005	0.016 ± 0.006	0.37 ± 0.23	0.63 ± 0.23
Temporal cortex	0.032 ± 0.002	0.013 ± 0.007	0.019 ± 0.006	0.40 ± 0.21	0.60 ± 0.21
Occipital cortex	0.038 ± 0.006†§	0.009 ± 0.004	0.029 ± 0.005†§§	0.24 ± 0.10	0.76 ± 0.10
Parietal cortex	0.030 ± 0.003‡**	0.014 ± 0.006	0.016 ± 0.006**	0.47 ± 0.20	0.53 ± 0.20
Cerebral cortices*	0.031 ± 0.003	0.011 ± 0.004	0.020 ± 0.002	0.37 ± 0.11	0.63 ± 0.11

Values are mean ± SD

*Average of frontal, temporal, occipital and parietal cortices

Significant difference in comparison to the frontal cortex (paired t-test): †$p < 0.01$, ‡$p < 0.05$

Significant difference in comparison to the temporal cortex (paired t-test): §$p < 0.01$, §§$p < 0.05$

Significant difference in comparison to the occipital cortex (paired t-test): **$p < 0.01$

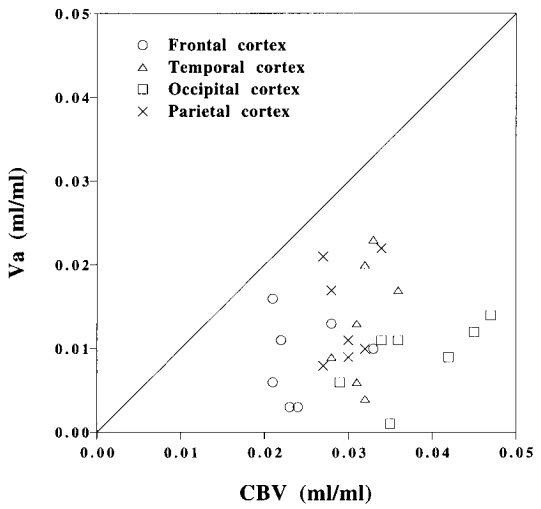

Fig. 3 The correlation between CBV and V_a.

to describe the time-activity curves. To compare the two models statistically, methods, the Akaike information criterion[18] and F-statistics[19] were used. Values are shown as mean ± SD.

RESULTS

Typical time-activity data for a cerebral cortical region and fitted curves determined by both the V_a and NoV_a models are shown in Figure 2. The regional time-activity data were well described by both models. The results of kinetic analyses for $H_2{}^{15}O$ PET are given in Table 1. The mean K_1 values obtained from the NoV_a model were significantly overestimated by 6% compared with those from the V_a model. The mean V_d values in the two models were identical. The Akaike information criteria (AIC) in the V_a model were significantly smaller than those in the NoV_a model, indicating the V_a model to be the preferred model. F-statistics also showed the V_a model to be preferred for each time-activity curve. Good correlation was observed in K_1 values was observed between the V_a and NoV_a models ($Y = 0.93X + 0.06$: X, V_a model; Y, NoV_a model; $r = 0.98$). The range of P_aCO_2 was 37.9 to 43.2 mm Hg for all subjects.

The CBV, V_a, and venous plus capillary blood volume ($V_v + V_c = CBV - V_a$, Eq. 1) values are given in Table 2. The average cerebral cortices CBV, V_a and $V_v + V_c$ were 0.031 ± 0.003 (ml/ml), 0.011 ± 0.004 (ml/ml) and 0.020 ± 0.002 (ml/ml), respectively. The arterial fraction of CBV (V_a/CBV) was 37 ± 11% that of the cerebral cortical average. The venous plus capillary fraction ($V_v + V_c$/CBV) was 63 ± 11%. The CBV value of the occipital cortex was significantly higher and the CBV value of the frontal cortex was significantly lower than the CBV value in the other regions. There were no significant differences between the regions in V_a values. No correlation between CBV and V_a was observed (Fig. 3).

DISCUSSION

Arterial fraction of cerebral blood volume

This is the first study to estimate the arterial fraction of CBV in the living human brain. The arterial fraction of CBV was 37% for the cerebral cortices (Table 2). This fraction was slightly greater than the arterial blood volume fraction for the systemic circulation of the whole body, which has been reported to be 20–30%.[20] In the measurement of $CMRO_2$ with a bolus inhalation of ^{15}O-labeled molecular oxygen ($^{15}O_2$) with PET, the arterial fraction of CBV is necessary for correction of intravascular radioactivity since the first-pass extraction fraction of $^{15}O_2$ is relatively high (about 40%).[2] According to the literature, the arterial fraction of CBV has been assumed to be 16% for this correction,[2] but this value was not for the brain. When an arterial fraction of 37% is used instead of 16%, the calculated $CMRO_2$ will be lowered. No correlation between CBV and V_a was observed (Fig. 3), indicating that V_a might be independent of CBV, but variations in V_a were larger than those of CBV since V_a is sensitive to statistical noise.

$H_2{}^{15}O$ is a tracer that can freely diffuse through the blood-brain barrier but, in fact, the capillary permeability-surface product of $H_2{}^{15}O$ is not infinite, indicating that the first-pass extraction fraction of $H_2{}^{15}O$ (E) is less than 1.[21,22] Since radioactivity in the capillary and vein become higher than that in the brain tissue when E is less than 1,[3] V_a is greater than the true intravascular volume of the artery. The V_a value obtained in the present study therefore includes a part of the intravascular volume of the capillary and vein. The true arterial fraction of CBV (X) is expressed with the first-pass extraction fraction of $H_2{}^{15}O$ (E) and estimated arterial fraction (37%) as follows:

$$X + (1 - X) \cdot (1 - E) = 0.37$$

Assuming E to be 0.9,[21,22] the true arterial fraction of CBV (X) will be 30%.

In the present study the small- to large-vessel hematocrit ratio was assumed to be 0.85, in order to calculate the CBV according to the method reported,[5] but this ratio has also been reported to be 0.69 as measured by PET in the human brain.[23] When the hematocrit ratio of 0.69 is used instead of 0.85, the CBV will become greater. The hematocrit ratio might not be uniform in the brain, and individual variation might exist. These may also cause errors in the determination of CBV. In addition, changes in cerebral hematocrit with cerebrovascular disease have been reported.[24]

Venous plus capillary fraction of cerebral blood volume

The venous plus capillary fraction of CBV was 63% for the cerebral cortices (Table 2). Considering limited first-pass extraction fraction of $H_2{}^{15}O$, the true venous plus capillary fraction of CBV is estimated to be about 70% as

mentioned above. Since the capillary bed is smaller in volume than the noncapillary bed, this fraction represents mainly the venous fraction.[2,8] The measurement of $CMRO_2$ using BOLD contrast with fMRI has recently been reported.[7] Since the concentration of oxygenated blood in venous and capillary blood is the main contributor to BOLD contrast,[6,8] the venous plus capillary fraction of CBV is a important factor for the measurement of $CMRO_2$ using BOLD contrast with fMRI.[7–9] The estimated value of venous plus capillary fraction of CBV in the present study can be used for such a measurement.

Comparison of the V_a and NoV_a models

Although the regional time-activities were well described by both the V_a and NoV_a models (Fig. 2), the AICs in the V_a model were significantly smaller than those in the NoV_a model, indicating the V_a model to be the preferred model.[3] F-statistics also showed the V_a model to be preferred. The K_1 obtained from the NoV_a model was significantly overestimated by 6% compared with K_1 from the V_a model, whereas the V_d was identical in the two models (Table 1) but a good correlation in K_1 values was observed between the V_a and the NoV_a models. Since V_a was small, the overestimation of K_1 for the NoV_a model which has widely been used to calculate CBF[16,17] would be small.

CONCLUSION

The arterial fraction of CBV was 37%. Considering a limited first-pass extraction fraction of $H_2{}^{15}O$, the true arterial fraction of CBV is estimated to be about 30%. This fraction quite similar to that for the systemic circulation of the whole body but higher than that widely used for the correction of intravascular radioactivity in the measurement of $CMRO_2$ with $^{15}O_2$ and PET. The venous plus capillary fraction of CBV was 63–70% which is an important factor for the measurement of $CMRO_2$ using BOLD contrast with fMRI.

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