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. C15O and dynamic H215O PET studies were performed in each of seven healthy subjects to determine the CBV and arterial blood volume (VA), respectively. A two-compartment model (influx: K1, efflux: k2) that takes VA into account was applied to describe the regional time-activity curve of dynamic H215O PET. K1, k2 and VA were calculated by a non-linear least squares fitting procedure. The VA and CBV values were 0.011 ± 0.004 ml/ml and 0.031 ± 0.003 ml/ml (mean ± SD), respectively, for cerebral cortices. The arterial fraction of CBV was 37%. Considering the limited first-pass extraction fraction of H215O, 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 (CMRO2) using PET. The venous plus capillary fraction of CBV was 63–70% which is an important factor for the measurement of CMRO2 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 components 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 15O-labeled carbon monoxide (C15O) 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 (CMRO2) by means of BOLD contrast 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 an important factor for 
the measurement of CMRO2 by means of BOLD contrast 
with fMRI.7-9 
15O-labeled water (H215O) is a tracer that can freely 
diffuse through the blood-brain barrier. After intravenous 
infusion of H215O, the radioactive 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 H215O.11 
Recently this two-compartment model has been applied 
to describe the regional time-activity curve of H215O in the 
brain.3 With this model, the arterial blood volume in a 
brain region can be calculated from dynamic H215O PET 
data.

In the present study we estimated the arterial fraction of 
CBV by means of PET in the living human brain. Both 
C15O and H215O PET studies were performed in each of 
seven healthy subjects. The CBV and arterial blood volume 
were determined from C15O and H215O 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

\[ CBV = V_A + V_C + V_V \]  
\( \text{(Eq. 1)} \)

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 H215O in the brain, the two-
compartment model that takes \( V_A \) into account (Fig. 1) is used. According to this model, the radioactivity 
concentration in a brain region can be expressed as 
follows.3,11

\[ C_a(t) = K_i \cdot C_b(t) \otimes e^{-k_2t} + V_A \cdot C_d(t) \]  
\( \text{(Eq. 2)} \)

where \( C_a(t) \) is the radioactivity concentration in a brain 
region, \( C_b(t) \) is the radioactivity concentration in the 
arterial whole blood (arterial input function), \( K_i \) is the 
influx rate constant (m/ml/min) and \( k_2 \) is the efflux rate 
constant (min⁻¹). The influx rate constant \( K_i \) corresponds 
to the cerebral blood flow (CBF). The \( K_i/k_2 \) ratio is 
defined as the distribution volume (V_A, 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 deter-
mined to be healthy based on their medical history, physical 
examination, blood screening analysis and MRI of the 

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.

C15O study
To measure the CBV, a C15O PET study was performed.5 
The static PET scan was started 3 minutes after 1 minute 
of continuous inhalation of C15O 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 C15O PET scanning.

H215O study
After the C15O PET study, 360-second dynamic scanning 
was performed following continuous intravenous 
infusion of H215O 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 func-
tion 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 CO2 
gaseous pressure. A head fixation system with individual 
molds for each subject was used to minimize head move-
ment over the period of the PET measurements.

Regions of interest
Regions of interest (ROIs) were drawn on the PET im-
ages. 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. 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 (No$V_a$ model) which has widely been used to calculate CBF 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.](image)

![Fig. 2 Typical time-activity data for a cerebral cortical region and fitted curves in both the $V_a$ and No$V_a$ model.](image)

<table>
<thead>
<tr>
<th>Table 1</th>
<th>The $K_i$, $V_d$ and Akaike information criterion (AIC) values obtained by kinetic analyses for $H_2^{15}$O PET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Region</td>
<td>$K_i$ (ml/ml/min)</td>
</tr>
<tr>
<td>-------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Frontal cortex</td>
<td>0.47 ± 0.10$^a$</td>
</tr>
<tr>
<td>Temporal cortex</td>
<td>0.52 ± 0.06$^a$</td>
</tr>
<tr>
<td>Occipital cortex</td>
<td>0.51 ± 0.06$^a$</td>
</tr>
<tr>
<td>Parietal cortex</td>
<td>0.49 ± 0.08$^a$</td>
</tr>
<tr>
<td>Cerebral cortices*</td>
<td>0.50 ± 0.07$^a$</td>
</tr>
</tbody>
</table>

Values are mean ± SD

$^a$Average of frontal, temporal, occipital and parietal cortices

Significant difference in comparison to the $V_a$ model (paired t-test): $^p < 0.01$, $^{hp} < 0.05$

<table>
<thead>
<tr>
<th>Table 2</th>
<th>The CBV, $V_a$, $V_r + V_c$ (= CBV − $V_a$) and arterial and venous plus capillary fraction of CBV ($V_r/CBV$, $V_r + V_c/CBV$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Region</td>
<td>CBV (ml/ml)</td>
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<tr>
<td>-------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Frontal cortex</td>
<td>0.025 ± 0.004</td>
</tr>
<tr>
<td>Temporal cortex</td>
<td>0.032 ± 0.002</td>
</tr>
<tr>
<td>Occipital cortex</td>
<td>0.038 ± 0.006$^{hp}$</td>
</tr>
<tr>
<td>Parietal cortex</td>
<td>0.030 ± 0.003$^{**}$</td>
</tr>
<tr>
<td>Cerebral cortices*</td>
<td>0.031 ± 0.003</td>
</tr>
</tbody>
</table>

Values are mean ± SD

$^a$Average of frontal, temporal, occipital and parietal cortices

Significant difference in comparison to the frontal cortex (paired t-test): $^p < 0.01$, $^{hp} < 0.05$

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

Significant difference in comparison to the occipital cortex (paired t-test): $^{**}p < 0.01$
to describe the time-activity curves. To compare the two models statistically, methods, the Akaike information criterion\textsuperscript{18} and F-statistics\textsuperscript{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\textsubscript{a} and NoV\textsubscript{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\textsubscript{2}15O PET are given in Table 1. The mean K\textsubscript{1} values obtained from the NoV\textsubscript{a} model were significantly overestimated by 6% compared with those from the V\textsubscript{a} model. The mean V\textsubscript{a} values in the two models were identical. The Akaike information criteria (AIC) in the V\textsubscript{a} model were significantly smaller than those in the NoV\textsubscript{a} model, indicating the V\textsubscript{a} model to be the preferred model. F-statistics also showed the V\textsubscript{a} model to be preferred for each time-activity curve. Good correlation was observed in K\textsubscript{1} values was observed between the V\textsubscript{a} and NoV\textsubscript{a} models (Y = 0.93X + 0.06; X, V\textsubscript{a} model; Y, NoV\textsubscript{a} model; r = 0.98). The range of P\textsubscript{a}CO\textsubscript{2} was 37.9 to 43.2 mm Hg for all subjects.

The CBV, V\textsubscript{a}, and venous plus capillary blood volume (V\textsubscript{e} + V\textsubscript{c} = CBV − V\textsubscript{a}, Eq. 1) values are given in Table 2. The average cerebral cortices CBV, V\textsubscript{a}, and V\textsubscript{e} + V\textsubscript{c} were 0.031 ± 0.003 (ml/mm\textsuperscript{3}), 0.011 ± 0.004 (ml/ml) and 0.020 ± 0.002 (ml/ml), respectively. The arterial fraction of CBV (V\textsubscript{a}/CBV) was 37 ± 11% of that of the cerebral cortical average. The venous plus capillary fraction (V\textsubscript{e} + V\textsubscript{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\textsubscript{a} values. No correlation between CBV and V\textsubscript{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%.\textsuperscript{20} In the measurement of CMRO\textsubscript{2} with a bolus inhalation of 15O-labeled molecular oxygen (15O\textsubscript{2}) with PET, the arterial fraction of CBV is necessary for correction of intravascular radioactivity since the first-pass extraction fraction of 15O\textsubscript{2} is relatively high (about 40%).\textsuperscript{2} According to the literature, the arterial fraction of CBV has been assumed to be 16% for this correction, but this value was not for the brain. When an arterial fraction of 37% is used instead of 16%, the calculated CMRO\textsubscript{2} will be lowered. No correlation between CBV and V\textsubscript{a} was observed (Fig. 3), indicating that V\textsubscript{a} might be independent of CBV, but variations in V\textsubscript{a} were larger than those of CBV since V\textsubscript{a} is sensitive to statistical noise.

H\textsubscript{2}15O is a tracer that can freely diffuse through the blood-brain barrier but, in fact, the capillary permeability-surface product of H\textsubscript{2}15O is not infinite, indicating that the first-pass extraction fraction of H\textsubscript{2}15O (E) is less than 1.\textsuperscript{21,22} Since radioactivity in the capillary and vein become higher than that in the brain tissue when E is less than 1,\textsuperscript{3} V\textsubscript{a} is greater than the true intravascular volume of the artery. The V\textsubscript{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\textsubscript{2}15O (E) and estimated arterial fraction (37%) as follows:

\[ X + (1 - X) \cdot (1 - E) = 0.37 \]

Assuming E to be 0.9,\textsuperscript{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,\textsuperscript{5} but this ratio has also been reported to be 0.69 as measured by PET in the human brain.\textsuperscript{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.\textsuperscript{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\textsubscript{2}15O, 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. The measurement of CMRO$_2$ using BOLD contrast with fMRI has recently been reported. Since the concentration of oxygenated blood in venous and capillary blood is the main contributor to BOLD contrast, the venous plus capillary fraction of CBV is an important factor for the measurement of CMRO$_2$ using BOLD contrast with fMRI. 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 No$V_a$ models

Although the regional time-activities were well described by both the $V_a$ and No$V_a$ models (Fig. 2), the AICs in the $V_a$ model were significantly smaller than those in the No$V_a$ model, indicating the $V_a$ model to be the preferred model. F-statistics also showed the $V_a$ model to be preferred. The $K_1$ obtained from the No$V_a$ model was significantly overestimated by 6% compared with $K_1$ from the $V_a$ model, whereas the $V_a$ was identical in the two models (Table 1) but a good correlation in $K_1$ values was observed between the $V_a$ and the No$V_a$ models. Since $V_a$ was small, the overestimation of $K_1$ for the No$V_a$ model which has widely been used to calculate CBF would be small.

CONCLUSION

The arterial fraction of CBV was 37%. Considering a limited first-pass extraction fraction of H$_2$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 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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REFERENCES


