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Title	Regional partition coefficient of water in patients with cerebrovascular disease and its effect on rCBF assessment
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Citation	Nuclear Medicine Communications, 32(1), 63-70 https://doi.org/10.1097/MNM.0b013e3283412106
Issue Date	2011-01
Doc URL	http://hdl.handle.net/2115/47945
Rights	This is a non-final version of an article published in final form in Nuclear Medicine Communications, Jan. 2011, 32(1), 63-70
Type	article (author version)
File Information	NMC32-1_63-70.pdf

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Title page

Regional partition coefficient of water in patients with cerebrovascular disease and its effect on rCBF assessment

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Running head: Partition Coefficient and CBF

Type of article: Original article

Source of Funding: None

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Abstract

Objective: Cerebral blood flow (CBF) estimation with $C^{15}O_2$ PET usually assumes a single tissue compartment model and a fixed brain-blood partition coefficient of water. However, the partition coefficient may change in pathologic conditions. The purpose of this study was to investigate the changes of partition coefficient of water in pathological regions and its effect on regional CBF assessment.

Methods: Study protocol included 22 patients with occlusive cerebrovascular disease to compare partition coefficients among 3 regions (infarction, non-infarct hypoperfusion, and contralateral) in the pathologic brain (analysis A), and to compare CBF estimated using fixed partition coefficient (CBFfixed) and CBF estimated using floating partition coefficients (CBFfloat) (analysis B).

Results: Partition coefficient in the infarction (0.55 ± 0.07 ml/g) was lower than that in contralateral normal cortex (0.68 ± 0.05 ml/g), while non-infarct hypoperfusion did not show a significant change (0.67 ± 0.06 ml/g). As a result, use of a fixed partition coefficient of normal volunteers (0.70 ml/g) resulted in an underestimation in rCBF by 12% in infarction area ($p < 0.05$), while estimation errors were smaller and induced no significant difference in non-infarct hypoperfusion area or in contralateral areas.

Conclusions: Partition coefficient is stable except for the infarction, and CBF estimation using a fixed partition coefficient of normal volunteers provides clinically appreciable information in patients with cerebrovascular disease.

Introduction

Cerebral blood flow (CBF) is an important indicator for severity and prognosis of patients with cerebrovascular diseases [1-3]. CBF quantification using $H^{15}O$ or $C^{15}O_2$ PET and a single tissue compartment model has been well established and widely applied in various clinical settings. Basic assumption for the single tissue compartment model includes (1) constant regional CBF during the study, (2) uniform tracer delivery to entire brain through cerebral arteries, and (3) free diffusion of water across the blood-brain barrier (BBB) resulting in the instantaneous distribution of the water in the brain tissues. In particular, distribution volume of water, so called brain-blood partition coefficient, is usually assumed to be constant in various pathology to simplify the model. A multicenter study revealed that 10 of 11 institutes used the methods with fixed partition coefficient ranging from 0.8 to 1.0 ml/g [4].

However, it is unclear whether partition coefficient of water is biologically stable under pathological conditions. Herscovitch et al. and Kudomi et al. suggested a possibility that partition coefficient might alter in edematous or necrotic tissues [5, 6]. A recent MR spectroscopy study investigated brain temperature and reported that ischemic brain tissues showed higher local temperature than non-ischemic tissues [7], which may affect regional partition coefficient [8]. Another study revealed ~40 % reduction of partition coefficient in the brain of the anesthetized baboon [9]. These lines of evidence suggest a possibility that brain-blood partition coefficient of water may not be stable in ischemic area of occlusive cerebrovascular disease.

The purpose of this study was to investigate the changes of partition coefficient of water in pathological regions and to elucidate errors in $C^{15}O_2$ PET derived CBF in pathological regions when using a fixed partition coefficient.

Materials and Methods

Study design

Seven healthy normal volunteers and 22 patients with unilateral cerebrovascular disease were retrospectively included for the study protocol. Patients were subjected to the following two analyses: (1) comparison of regional partition coefficient among normal and pathological areas to investigate the changes of partition coefficient of water in pathological regions (Analysis A), and (2) comparison between CBF estimated using floating partition coefficient (CBFfloat) and CBF estimated using fixed partition coefficient (CBFfixed) using $C^{15}O$ and $C^{15}O_2$ PET to elucidate errors in $C^{15}O_2$ PET-derived CBF in pathological regions when partition coefficient is fixed (Analysis B). The Ethics Committee of the Hokkaido University Hospital approved the study (#009-0310).

Subjects

The study protocol included the patients with (1) unilateral stenosis (> 70%) in either right or left internal carotid artery (ICA), and (2) unilateral stenosis (> 50%) in either right

or left middle cerebral artery (MCA). Patients with bilaterally involved cerebrovascular

disease (> 50% stenosis in either ICA or MCA), and patients with a history of cerebral

hemorrhage or traumatic brain injury were excluded from the analysis. The final study

population included a total of 22 patients (18 men and 4 women, aged 36-84 years, mean

age 63.3 ± 12.1 years) with unilateral cerebrovascular disease. The control group

consisted of seven healthy men (aged 23-40 years, mean age 30.6 ± 6.3 years)

volunteering to participate in this study. All volunteers underwent a series of MRI to

confirm no significant cerebrovascular disease.

Image Acquisition

All subjects underwent the same protocol of PET acquisition with $C^{15}O$ gas followed by

$C^{15}O_2$ gas inhalation technique, combined with arterial blood sampling to estimate

regional CBF quantitatively using a single tissue compartment model [10]. The

acquisition protocol employed a high-resolution PET scanner (ECAT HR+ scanner;

Asahi-Siemens Medical Technologies Ltd., Tokyo, Japan) operated in a two-dimensional

brain acquisition mode. Transmission datasets were acquired for the period of 5 min using

a $^{68}Ge/^{68}Ga$ retractable line sources. After preparing the patients for a standard gas

delivery system, 2.0 GBq/min of $C^{15}O$ gas was given through the system for 1 min. We

asked the patients to be awake and breathe normally. A static emission scan was initiated

after a waiting period of 3 min for $C^{15}O$ to combine with hemoglobin. Arterial blood

samples were drawn every minute from the right radial artery for a total of 3 samples to

obtain a mean arterial concentration of hemoglobin-bound $C^{15}O$ to calculate cerebral

blood volume (CBV). An automatic cross-calibrated γ-counter equipped with weighing

system (ARC-400; ALOKA Co., Ltd., Tokyo, Japan) measured the concentration of

radioactivity of the sampled arterial blood. The next emission scan using $C^{15}O_2$ gas

started 2 min after the completion of the $C^{15}O$ acquisition. For the $C^{15}O_2$ gas study, a

dynamic emission scan was initiated at the same time with the initiation of tracer delivery

using 1.5 GBq/min of $C^{15}O_2$ for 90 sec. The acquisition protocol included 17 frames,

consisting of 1×30 sec, 10×15 sec, and 6×30 sec frames. The initial dynamic frame

was longer than the following frames to allow proper scatter correction using the

algorithm implemented in the PET scanner. Arterial blood was sampled at 30, 45, 60, 75,

90, 105, 120, 135, 150, 165, 180, 210, 240, 270, 300, and 360 sec to obtain an individual

arterial input function of $H_2^{15}O$. All acquired data from PET were reconstructed using

direct inversion Fourier transformation method [11] with a Hann filter of 14 mm full

width half maximum. The reconstruction matrix was 256×256, and the FOV was 33 cm

in diameter. Sixty-three transaxial slices with a thickness of 2.4 mm were generated. Data

were corrected for dead time, decay, and measured photon attenuation.

Data Processing

Regional CBV was estimated on a pixel-by-pixel basis by the following formula to

generate parametric images:

$$CBV = P_{CO} / a_{co} / 0.85, \quad (1)$$

where P_{CO} is PET-produced $C^{15}O$ radioactivity concentration, a_{co} is arterial blood $C^{15}O$ radioactivity concentration, and 0.85 is the ratio of cerebral small-vessel to large-vessel hematocrit [12, 13].

The acquired arterial input function was corrected for delay of tracer delivery. A fixed delay of 10 seconds was applied for the present acquisition protocol, which was estimated from the previously published reports [15] and our previous investigations on the delay between the radial artery and the brain tissues.

Inhaled $C^{15}O_2$ is rapidly converted into $H_2^{15}O$ in the lung (chemical equation (2)). Then, the $H_2^{15}O$ circulates throughout the body and reaches the brain within 30 sec after tracer inhalation.

$$C^{15}O_2 + H_2O \leftrightarrow CO_2 + H_2^{15}O \quad (2)$$

Using a single tissue compartment model [14-16], the regional cerebral radioactivity is expressed by the following differential equation:

$$db(t)/dt = K_1a(t)-k_2b(t), \quad (3)$$

where b(t) is the decay-corrected radioactivity concentration in brain tissues at time t, and a(t) is that in the artery. K_1 and k_2 are rate constants, and K_1/k_2 represents brain-blood partition coefficient of water. Solving equation (3) about b(t) gives us

$$b(t) = K_1a(t) \otimes \exp(-k_2t). \quad (4)$$

$\otimes$ means convolution integral. PET-produced radioactivity represents a total radioactivity in a pixel, containing the radioactivity not only in tissues but also in vascular spaces. Therefore, using an established CBV correction method [9], theoretical

PET-produced radioactivity P(t) at time t is expressed as

$$P(t) = CBV\ a(t) + (1\text{-}CBV)\ b(t). \qquad (5)$$

To evaluate regional partition coefficient (analysis A), two variables including K_1 and k_2 were simultaneously determined by fitting P(t) to the acquired PET-producing time activity curve using nonlinear least square method on a pixel-by-pixel basis. To compare CBFfixed with CBFfloat (analysis B), we obtained equation (6) by replacing k_2 with K_1/ρ (ρ: partition coefficient, a constant value).

$$b(t) = K_1 a\ (t) \otimes \exp(\text{-}K_1\ t\ /\rho). \qquad (6)$$

Then, nonlinear least square method determined K_1 as the sole variable. For fixed ρ, the averaged value of healthy subjects was applied. In this study, we assumed extraction fraction of water to be 1, thus K_1 was equal to CBF. Dispersion was not corrected because of slow tracer delivery with the gas inhalation system. Calculation was performed with the program developed in our institute using Microsoft Visual C++ 6.0 for Windows.

Regions of Interest

Parametric images were generated for CBV, CBF and partition coefficient using the pixel-by-pixel information, which were anatomically coregistered to individual MR images using a mutual information algorithm implemented in NEUROSTAT software package [17, 18]. For region of interest (ROI) placement, the following regions were identified on the coregistered MR FLAIR images on each patient with cerebrovascular

disease: (1) infarction area, (2) non-infarct hypoperfusion area, and (3) contralateral area. Infarction area was defined as the cerebral region with the finding of high signal intensity on MR FLIAR image. The infarction areas smaller than 15 mm in diameter or smaller than 15 mm in z-axis dimension were excluded from the analyses. The non-infarct hypoperfusion area was defined as a cortex corresponding to the MCA territory of disease side on the level of centrum semiovale. In 9/22 patients presenting with cerebral infarction, the ROIs for non-infarct hypoperfusion were carefully placed on the region at least 15 mm distant from the infarction area in the same hemisphere. Contralateral area was defined as the normal-appearing cortex in the contralateral hemisphere of the non-infarct hypoperfusion area. A well trained nuclear medicine physician manually placed multiple uniform ROIs, each with circular shape and 15 mm in diameter, in the following fashion described as below; first, 3 ROIs (1 ROI on each the 3 axial slices) on infarction area only for the patients having infarction area meeting the criteria written above, then nine ROIs (3 ROIs on each the 3 axial slices) on non-infarct hypoperfusion area for all the patients, and finally nine ROIs (3 ROIs on each the 3 axial slices) on contralateral area for all the patients. The values of ROIs were averaged to obtain quantitative parameters of infarction, non-infarct hypoperfusion and contralateral areas, respectively. In healthy subjects, a total of 18 ROIs were placed in the bilateral cerebral cortex corresponding to MCA territories on the level of centrum semiovale (9 ROIs on each hemisphere). Individual normal control values of the quantitative parameters were calculated as an average of 18 ROIs.

Statistical analysis

Data were expressed as means ± 1 SD. Partition coefficients among the 3 regions of the

patients were compared using the one-way analysis of variance (ANOVA). When a

significant difference was observed, Tukey-Kramer post hoc test was further performed

to identify pairs showing significant differences. The CBFfloat and the CBFfixed were

compared using Pearson's correlation analysis, and Bland-Altman plot. Difference

between the mean values of CBFfloat vs. CBFfixed was analyzed with the paired *t*-test.

P-values less than 0.05 were considered to be statistically significant.

Results

Partition coefficients in normal and pathological brain (Analysis A)

The parametric images of healthy normal volunteers showed uniform partition coefficient

in the cerebral cortex. With the present acquisition protocol, the average cortical value of

partition coefficient was 0.70 ± 0.04 ml/g ranging from 0.65 to 0.76 ml/g, corresponding

to CBFfloat of 44.6 ± 8.2 ml/100 g/min ranging from 36.6 to 59.5 ml/100g/min.

In the pathological brain with cerebrovascular disease, parametric images

demonstrated visual heterogeneity in partition coefficient. In particular, infarction area

showed significantly lower partition coefficient, while the remaining cerebral cortex

showed relatively uniform value, including non-infarct hypoperfusion and contralateral

cortex (Figure 1). One-way ANOVA showed a significant difference among the groups,

with the estimated partition coefficient of 0.55 ± 0.07 ml/g in infarction, 0.67 ± 0.06 ml/g

in non-infarct hypoperfusion, and 0.68 ± 0.05 ml/g in contralateral area, respectively. Post hoc analysis showed significantly lower partition coefficient in the infarction than that of other regions (P<0.001 for both). Figure 2 and 3 show parametric images of representative cases with and without cerebral infarction (Fig. 2 and 3).

Errors in estimating CBF using a fixed partition coefficient (Analysis B)

Table 1 compares rCBF estimated using pixel-by-pixel value of partition coefficient (CBFfloat) and using a fixed partition coefficient of 0.70, corresponding to the average partition coefficient of cerebral cortex in healthy normal volunteers (CBFfixed) (Table 1). In infarction area, there was 12% underestimation in rCBF using a fixed partition coefficient, as a result of 21% difference (0.55 vs. 0.70 ml/g) in partition coefficient. Estimation errors were smaller in non-infarct hypoperfusion area or in contralateral areas, and there was no significant difference between the two rCBF measurements for these regions. The two rCBF estimations closely correlated with (R = 0.95, p < 0.001), or without (R = 0.92, p < 0.001) infarction area (Fig. 4a), although the Bland-Altman plot demonstrated a trend of underestimation in the low CBF regions (Fig. 4b). The mean difference of CBFfixed and CBFfloat did not show a significant estimation error. However, the difference between the two CBF measurements tended to be larger in high-flow areas. Figure 5 shows representative parametric images visualizing differences in regional CBF values between the two estimation methods. Perfusion abnormality in severely hypoperfused infarction area appeared more pronounced in CBFfixed than in

CBFfloat, while the two images were visually comparable in mild hypoperfusion and normal areas.

Discussion

The brain-blood partition coefficient of water was significantly lower in the infarction area but similar between (1) non-infarct hypoperfusion area and (2) contralateral area of patients with cerebrovascular disease. Patients' CBF calculated using a fixed partition coefficient of normal volunteer closely correlated with CBF calculated using floating partition coefficients without systematic over- or under-estimation except for infarction areas.

When partition coefficient was compared among different regional pathological conditions, only infarction areas showed a different partition coefficient, which was 18% smaller than the non-infarct hypoperfusion area, and 19% smaller than the contralateral cortex. The estimated partition coefficient of non-infarct hypoperfusion and contralateral side did not differ significantly. The smaller partition coefficient in the infarction most likely represents decreased cellular components of brain tissues. In a single tissue compartment model, the brain-blood partition coefficient of water is expressed as a ratio of K_1/k_2, where K_1 is the rate constant from blood vessel to brain tissue, and k_2 is the rate constant from brain tissue to blood vessel, respectively. Therefore, partition coefficient biologically represents the distribution volume of water per unit of cellular component of the brain. Cerebral infarction is likely to reduce cellular component and to increase

extra-cellular space per unit of brain volume, causing the decreased distribution volume of the water. In the non-infarct hypoperfusion areas, the present results did not show a significant change in the partition coefficient. The non-infarct hypoperfusion areas probably preserve cellular components. Previous studies with ^{11}C-flumazenil observed preserved neuronal integrity in hypoperfused areas reporting ~80 % of binding potential compared to control [19, 20].

Recent experimental study suggested a new mechanism of cerebral water distribution, which is not implemented in the present single tissue compartment model. Instead of direct water exchange between capillary space and neurons, they suggested a role of aquaporin (AQP) 4, which is expressed on the surface of astroglial cells and regulates water movements between capillary space and astroglial cells [21, 22]. The water movement through AQP4 may not follow diffusion mechanism of water, which may affect water kinetics considering the number of astroglial cells which is 1.6 times greater than the neurons in the human brain [23]. Although water exchange through AQP4 is less likely to affect the distribution volume in the pathologic condition since astroglial cells are known to be resistant to ischemic damage, future study should investigate the possible mechanism of water distribution which is not implemented in the present single-tissue compartment model.

The present study also investigated the errors in estimating CBF using a fixed partition coefficient of healthy normal volunteers. CBFfixed demonstrated a good agreement with CBFfloat in contralateral cortex and non-infarct hypoperfusion areas,

while it underestimated the rCBF of the infarction by 12%, due to decreased regional

partition coefficient. We employed the value of 0.70 ml/g for a fixed partition coefficient,

based on the averaged partition coefficient of the normal healthy brains. The value of

partition coefficient varies depending on the specifications of the equipment in addition to

acquisition and reconstruction protocol, thus requires an institutional normal value

calculated using the same protocol with the investigated patients. The fixed partition

coefficient of 0.70 ml/g was lower than theoretically calculated values of 0.99 ml/g in

cerebral cortex [24] most likely due to limited spatial resolution of the present clinical

imaging protocol. We applied relatively strong smoothing filters (FWHM = 14mm) for

image reconstruction before compartmental analysis to minimize statistical noise, and

obtained clinically appreciable parametric images. The smoothing operation caused

underestimation of partition coefficient via amplified partial volume effects, which would

include mixture of tissues with low partition coefficient, such as white matter and CSF

[24].

CBFfixed underestimated rCBF in the cerebral infarction, but the degree of the

underestimation did not affect overall correlation due to extremely low CBF in the

infarction areas in either measurement, attenuating the error of fixed partition coefficient

in low-flow areas. Since accurate CBF assessment is critical in high risk areas without

cerebral infarction, simple CBF measurement with fixed partition coefficient is

acceptable in most of clinical settings. However, one should pay attention to the slight

underestimation of CBFfixed in the infarction due to overestimated partition coefficient.

The present study has the following limitations. First, we targeted only unilateral occlusive cerebrovascular disease. Other neurological disorders may have different mechanism of altered partition coefficient from cerebrovascular disease. Degenerative disorder of Alzheimer disease, for example, may have a possible alteration in partition coefficient due to functional changes in neurons in addition to reduced number of neurons per unit of brain tissue. Second, the absolute value of partition coefficient cannot be compared with the previously published numbers due to possible difference in acquisition and reconstruction protocol. We applied relatively strong smoothing filters for image reconstruction for clinical purpose, which explains the lower value compared to the previously reported value in human [16]. In addition, the present acquisition protocol used a slow inhalation of $C^{15}O_2$, which has a different characteristics in kinetic in the single tissue compartment model compared with that of $H_2^{15}O$ bolus infusion protocol. A slow inhalation of $C^{15}O_2$ is relatively independent from dispersion because of the shape of the input function presenting with less steep slopes around the peak. In addition, it also allows the use of fixed delay time due to stable delay between radial and cerebral arteries [16, 25].

Clinical implication of this work supports the use of fixed partition coefficient for CBF estimation in patients with unilateral cerebrovascular disease to investigate rCBF of non-infarct areas. The current study validates the accumulated lines of clinical evidence regarding CBF in cerebrovascular disease since 1980s using fixed partition coefficient [26-28], although the areas of infarction might underestimate rCBF due to

overestimated partition coefficient.

In summary, brain-blood partition coefficient of water was reduced in the cerebral infarction, but was not significantly altered in the non-infarct hypoperfusion areas of unilateral cerebrovascular disease. The CBF estimated using a fixed partition coefficient underestimated the rCBF in the cerebral infarction by 12 % due to overestimated partition coefficient. Since rCBF of infarction was low, it did not affect overall estimation of rCBF. In conclusion, partition coefficient is stable except for the infarction, and CBF estimation using a fixed partition coefficient provides clinically appreciable information in patients with cerebrovascular disease.

Table 1. CBF calculated using floating partition coefficient and a fixed partition coefficient

	CBFfloat (ml/100 g/min) [a]	CBFfixed (ml/100 g/min) [b]	P-value [c]
Infarction area (n = 9)	21.3 ± 7.0	18.7 ± 7.5	<0.001
Non-infarct hypoperfusion area (n = 22)	33.2 ± 8.0	33.0 ± 9.2	0.78
Contralateral area (n = 22)	39.5 ± 8.1	39.5 ± 9.7	0.99

[a] CBFfloat was calculated using floating partition coefficient. [b] CBFfixed was calculated using a fixed partition coefficient as 0.70 ml/g. [c] P-value was calculated using paired *t*-test. Data are presented as mean ± SD.

Figure Legends

Fig. 1

Partition coefficient among infarction area (n = 9), non-infarct hypoperfusion area (n = 22), and contralateral area (n = 22). ANOVA and a Tukey-Kramer post hoc test detected significant difference between infarction area (*) and any other regions (P < 0.001).

Fig. 2

A representative case without cortical infarction (case 1). The patient had an occluded right internal carotid artery. **a** CBF (0-60.0 ml/100 g/min), **b** partition coefficient (0-1.0 ml/g), **c** MR FLAIR image.

Fig. 3

A patient with cerebral infarction showing low partition coefficient in the infarction area (case 2). **a** CBF (0-60.0 ml/100 g/min), **b** partition coefficient (0-1.0 ml/g), **c** MR FLAIR image.

Fig. 4

a Correlation of CBFfloat and CBFfixed. Solid line, regression (R = 0.95 with all regions included); dotted line, the line-of-identity. **b** Bland-Altman plot. Solid line, mean difference; dotted line, the line-of-identity; and dashed lines, mean ± 2 SD (-0.5 ± 7.4

ml/100 g/min).

Fig. 5

Representative parametric images of **a** CBFfloat and **b** CBFfixed showing comparable

values.

Conflict of interest

The authors declare that they have no conflict of interest.

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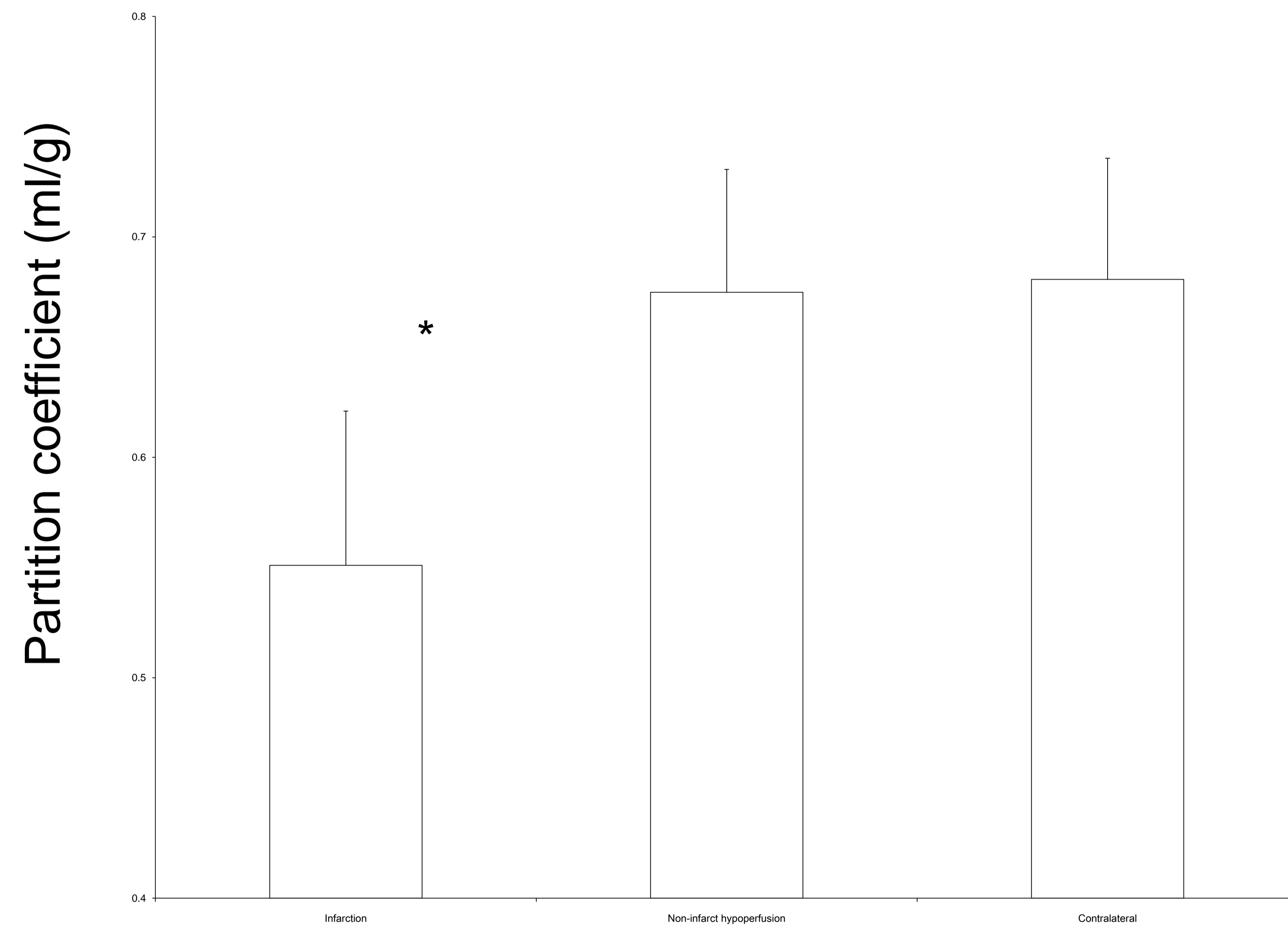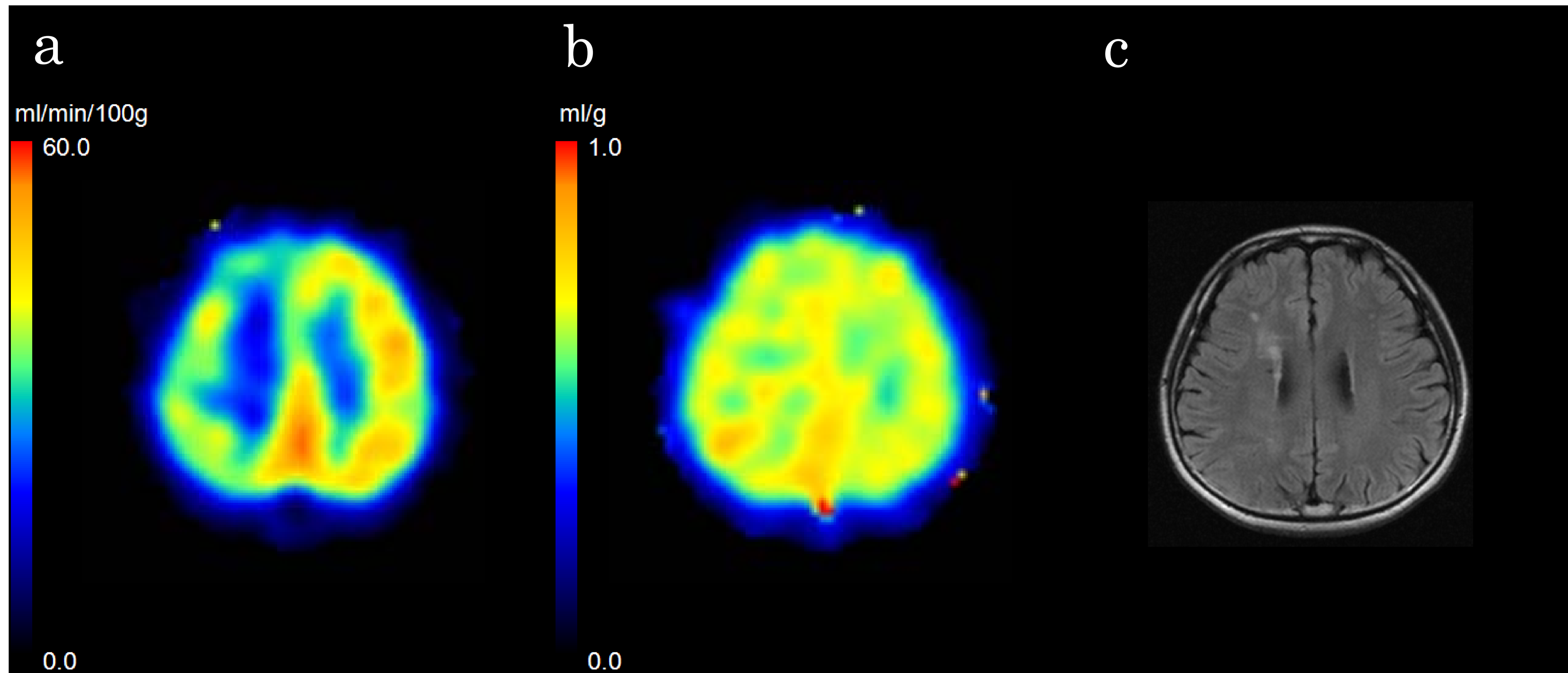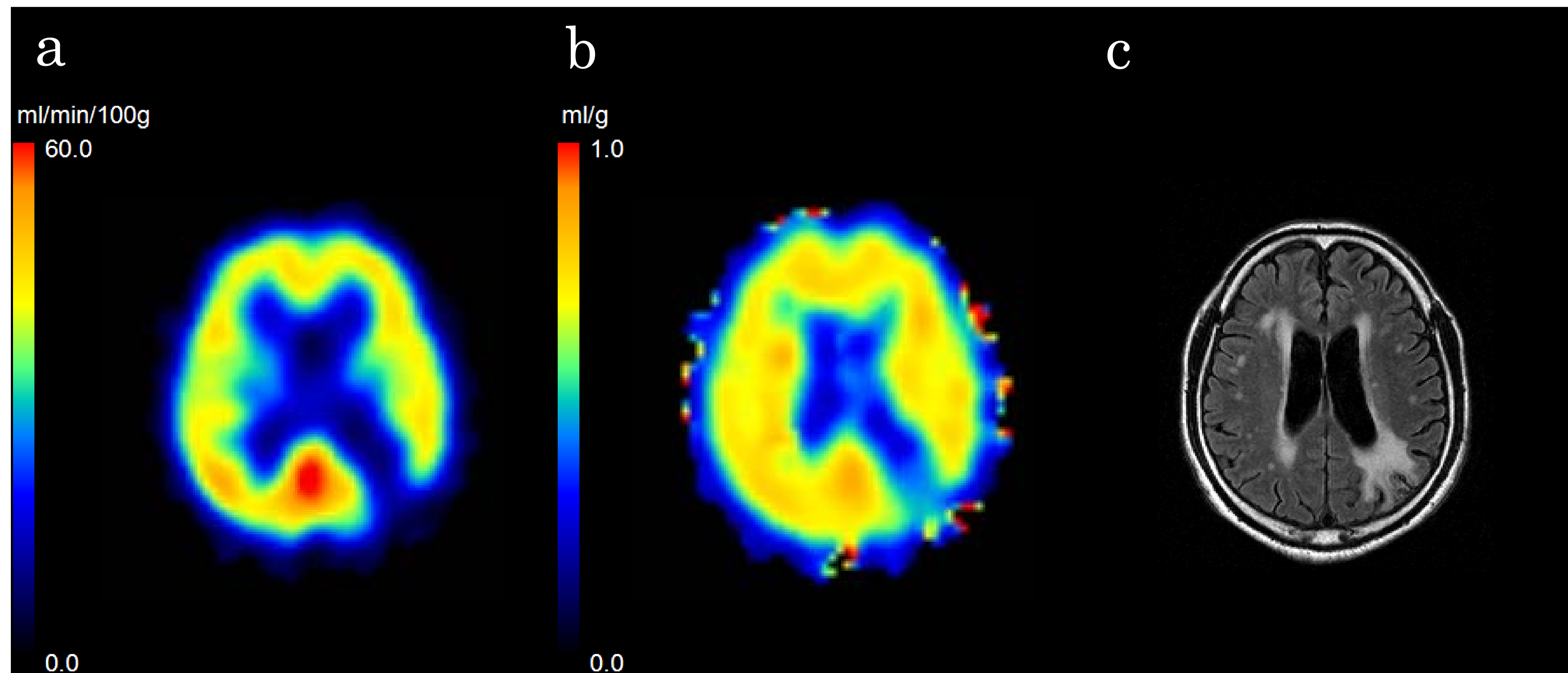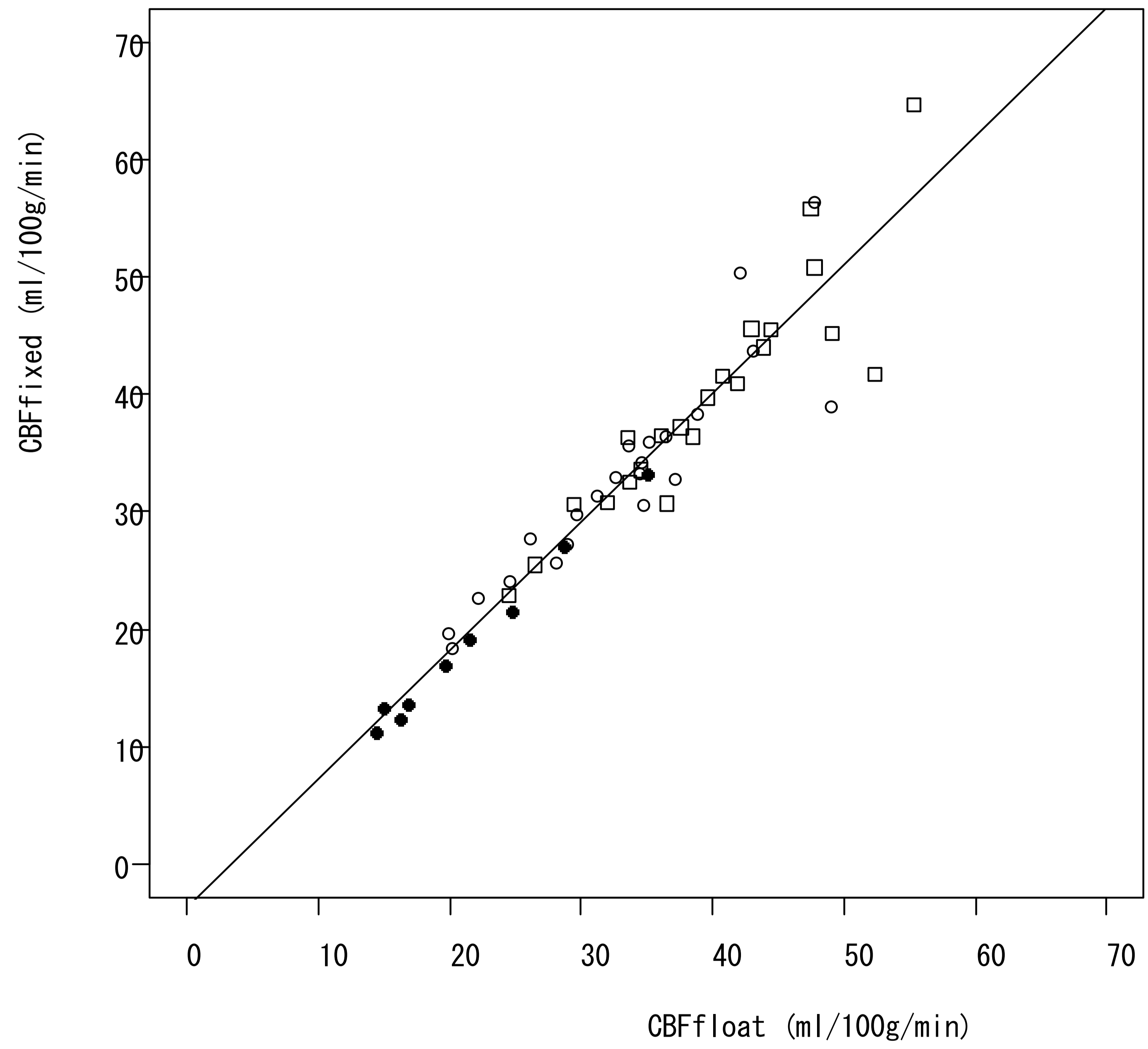
Fig. 1

Fig. 2

Fig. 3

Fig. 5