Diagnosis of misery perfusion using noninvasive 150-gas PET.

Diagnosis of misery perfusion using noninvasive O-15 gas PET.

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ABSTRACT

To avoid arterial blood sampling and complicated analyses in ^{15}O-gas PET studies, noninvasive technique using the count-based method was evaluated for the measurement of asymmetric OEF increase in cerebrovascular disease. **Methods:** Eighteen patients (61±16 y) with atherothrombotic large cerebral arterial disease were studied for the measurement of hemodynamic parameters using the ^{15}O-gas steady-state method with inhalation of $^{15}O_2$, $C^{15}O_2$ and $C^{15}O$. All patients also underwent $H_2{}^{15}O$-PET with the bolus injection method. Count-based ratio images of $^{15}O_2/C^{15}O_2$ and $^{15}O_2/H_2{}^{15}O$ were calculated and asymmetry indexes (AI) were obtained ($cbOEF_{SS}$-AI and $cbOEF_{BO}$-AI, respectively) using the regions of interest drawn on the bilateral cerebral cortices. These AI were compared with AI of absolute OEF (qOEF-AI) as well as those after cerebral blood volume (CBV) correction. A contribution factor for this correction was defined as variable α, and the effect of the correction was evaluated. **Results:** $cbOEF_{SS}$-AI underestimated qOEF-AI significantly, especially with a greater AI ($P < 0.05$). $cbOEF_{BO}$-AI linearly correlated well with qOEF-AI. CBV correction improved slopes of regression lines between qOEF-AI and $cbOEF_{SS}$-AI, and the optimal α was defined as 0.5. On the other hand, $cbOEF_{BO}$-AI fairly estimated qOEF-AI without CBV correction. Correlation coefficients between qOEF-AI and $cbOEF_{BO}$-AI were adversely affected and the mean bias increased with a greater α. **Conclusion:** $cbOEF_{BO}$-AI can fairly estimate AI of OEF without CBV correction, whereas $cbOEF_{SS}$-AI might require CBV correction for better estimation. The count-based method would reduce the examination time and stress to patients because of the noninvasive procedure.

Key words: Oxygen extraction fraction; misery perfusion; gas PET study; noninvasive method; cerebrovascular disease.

INTRODUCTION

Measurement of the cerebral oxygen extraction fraction (OEF) with positron emission tomography (PET) provides information on the hemodynamic status of patients with cerebrovascular disease (CVD). Misery perfusion, defined by an increase in OEF in the ischemic brain region (*1-5*), is caused by a decrease in cerebral blood flow (CBF), presumably due to a reduction in cerebral perfusion pressure and disturbance of cerebral autoregulation. Because patients with misery perfusion in stage II ischemia are considered to have a significantly higher stroke recurrence ratio than those without misery perfusion (*2,5,6*), it is important to evaluate the hemodynamic status of those patients with atherothrombotic large cerebral arterial occlusive disease whether neurosurgical treatment is needed or not.

Several methods for measurement of quantitative OEF (qOEF) with PET have been developed and used (*3,4,8-12*). The steady-state method with inhalation of ^{15}O-gas is widely used in Japan as a simple and practical method for measurement of CBF, OEF and cerebral metabolic rate of oxygen ($CMRO_2$) (*3,8*). Mintun et al. developed the three step method with the bolus injection of ^{15}O-water and bolus inhalation of $^{15}O_2$ to measure cerebral hemodynamic parameters (4). These methods for qOEF measurement are used for evaluation of hemodynamic impairment; however, they require arterial blood sampling during PET examination. It is an invasive and time-consuming procedure to take an arterial line before PET studies and exposes the patient to unnecessary risks (*13-15*). This is the reason why the simple method of count-based measurement of OEF has been proposed and is expected to be a substitute method for detection of misery perfusion (*14*,16).

The purpose of this study was to evaluate whether the count-based method for OEF measurement can detect misery perfusion correctly in the affected cerebral

regions of patients with chronic CVD. The count-based OEF (cbOEF) method can noninvasively evaluate asymmetric increases of OEF with a very simple calculation process (*14-16*). However, the method for this semi-quantitative assessment has not been sufficiently established as to which method for tracer administration and image calculation is appropriate for evaluation of side-to-side OEF differences to detect misery perfusion. In the present study, cbOEFs obtained from two methods of the continuous ^{15}O-gas inhalation and the bolus $H_2{}^{15}O$ injection were applied to calculate left-to-right ratios of OEF in patients with symptomatic severe stenoocclusive disease in the major cerebral arteries. The effect of CBV correction on cbOEF was also evaluated in both methods.

MATERIALS AND METHODS

Subjects

The study consisted of 18 patients (16 males and 2 females; mean age = 61 ± 16 y) with ischemic cerebrovascular disease. Seventeen had lesions of occlusion (n = 8) or stenosis (n = 9, greater than 70% diameter reduction) in the unilateral internal carotid artery (ICA; n = 16) or the middle cerebral artery (MCA; n = 1). The remaining patient had stenotic lesions in the right ICA and left MCA. Six had suffered transient ischemic attacks (TIA), ten had had a nondisabling hemispheric stroke with minor cerebral infarction on MRI, and two had no neurological symptoms. The interval between the latest ischemic event and the individual PET scan ranged from 3.4 ± 3.7 months. They underwent MRI, MR angiography and/or conventional angiography to examine any and all cerebral and arterial lesions. The percent reduction in diameter of stenotic lesions was measured by conventional

angiography and/or ultrasonography in the cervical lesions and by conventional angiography in the intracranial lesions. The study was approved by the Ethical Committee of the University of Fukui, Faculty of Medicine. Written informed consent was obtained from each subject before the study.

Positron Emission Tomography Procedures

All patients underwent PET scans with a whole-body tomography scanner (ADVANCE; General Electric Medical System, Milwaukee, WI), which permits simultaneous acquisition of 35 image slices with an interslice spacing of 4.25 mm (17). Performance tests showed the intrinsic resolution of the scanner to be 4.6 to 5.7 mm in the transaxial direction and 4.0 to 5.3 mm in the axial direction. A transmission scan was performed for 10 min using the $^{68}Ge/^{68}Ga$ line source for attenuation correction in each subject before tracer administration. All emission scans were acquired in a two-dimensional mode. The PET data were reconstructed using a Hanning filter with a resolution of 6.0 mm full width at half maximum in the transaxial direction.

Patients were positioned on the scanner bed with their heads immobilized using a head holder. A small cannula was placed in the right brachial artery for blood sampling. In the steady-state method, $^{15}O_2$ (740 MBq/min) and $C^{15}O_2$ (370 MBq/min) were inhaled continuously for approximately 8 min, and static PET scans were started and continued for 5 min to calculate images of CBF, OEF and $CMRO_2$ (*3,8,18*). Each subject also inhaled $C^{15}O$ as a single dose of 1000 MBq for CBV measurement (18). The PET scan was started after at least 30 sec from the arrival of the peak count of tracer in the brain and continued for 3 min. Arterial blood was sampled two or three times during each procedure of the ^{15}O-gas study to measure

quantitative hemodynamic parameters. The radioactivity in the blood samples thus obtained was immediately measured with a scintillation counter to determine arterial blood activity. During continuous inhalation of $^{15}O_2$ in the steady-state method, the sampled blood was divided into two aliquots to count the radioactivity of whole blood and plasma. Before the ^{15}O-gas scans, all patients also underwent $H_2{}^{15}O$ PET scans with a 3-min acquisition started at the time of bolus injection of the tracer (740 MBq). This data was used for calculation of the count-based OEF image (*14,16*). To reduce influence of intravascular radioactivity, initial frames (about 30 sec) of dynamic PET data were eliminated in the $H_2{}^{15}O$ bolus scan before count summation (19).

Absolute values of CBF, CBV, OEF and $CMRO_2$ were obtained from image calculation of the steady-state method (*3,8*). A cerebral-to-large vessel hematocrit ratio of 0.85 was used in the calculation of CBV (*20,21*). The individual CBV image thus obtained was used for correction of the quantitative OEF image to reduce the effect of radioactivity in the cerebral vessels (8). Total arterial O_2 content measured from the arterial blood sampled in each $^{15}O_2$ scanning was used in calculation of the $CMRO_2$ image.

Data Analysis

Regional values were obtained from regions of interest (ROIs) drawn on the cerebral cortices in the bilateral hemisphere using three slices. Elliptical ROIs at 15 x 50 mm were placed on cortical territories of the bilateral MCA at the level of the centrum semiovale (Fig. 1). Before placing ROIs, images of hemodynamic parameters and individual MRI were normalized anatomically in each subject using SPM2 (The Wellcome Dept. of Imaging Neurology, London). The ROIs placed in

the ipsilateral hemisphere using normalized MRI were copied symmetrically at correspondent regions of the contralateral hemisphere in the standard brain space. In patients with cerebral infarction, the ROIs were placed avoiding the area of infarction on the normalized individual MR images. The same ROIs were applied to all parametric images in each subject. The values obtained from the ROIs were averaged in each hemisphere.

The cbOEF images were obtained from simple pixel-by-pixel calculation of count ratios by $^{15}O_2/C^{15}O_2$ ($cbOEF_{SS}$) and $^{15}O_2/H_2{}^{15}O$ ($cbOEF_{BO}$). The asymmetry index (AI = [ipsilateral] / [contralateral]) of regional OEF was obtained from the cbOEF image ($cbOEF_{SS}$-AI and $cbOEF_{BO}$-AI, respectively). The values of cbOEF-AI were compared with that of absolute OEF (qOEF-AI). Because qOEF was corrected for the influence of blood volume using CBV image, blood volume correction was considered to be needed for cbOEF to achieve a better correlation with qOEF. To remove the influence of blood volume on regional values, the cbOEF was corrected using counts of the $C^{15}O$ image (Bq/ g) with the following equation, which was modified and simplified from the method of CBV correction for absolute OEF by Lammertsma et al. (*8*):

$$\mathrm{cbOEF_C} = \frac{cbOEF - \alpha \cdot \mathrm{X}_{CO}}{1 - \alpha \cdot \mathrm{X}co} \qquad \text{Eq.1}$$

$$\mathrm{X_{CO}} = \frac{C_{CO2} / S_{CO}}{C_{CO2} / C_{CO}} \quad [\text{or} \quad \frac{C_{H2O} / S_{CO}}{C_{H2O} / C_{CO}}] \qquad \text{Eq.2}$$

where $cbOEF_C$ is the corrected cbOEF, α is a contribution factor for the blood volume correction in the count-based method, S_{CO} (Bq/ g) is the regional value in the sagittal sinus obtained from ROIs on the $C^{15}O$ image, and C_{CO2}, C_{H2O} and C_{CO} are regional counts in the $C^{15}O_2$, $H_2{}^{15}O$ or $C^{15}O$ images, respectively. To determine S_{CO},

three small circular ROIs (5 mm in diameter) were drawn on the sagittal sinus using the $C^{15}O$ image, and the mean of the ROI counts was assumed to be 1 (mL/ g) because the sinus should include only blood (21). The effect of α on $cbOEF_C$ was evaluated with an assumption that this factor would have an optimal value for correction of blood volume because X_{CO} should be affected by a partial volume effect of the sagittal sinus and image resolution. Correlation coefficients between qOEF-AI vs. $cbOEF_C$-AI, and the mean distance of all plots from the line of identity (bias) were calculated as a function of α.

Differences between qOEF-AI and $cbOEF_{SS}$-AI or $cbOEF_{BO}$-AI were compared statistically using repeated-measured analysis of variance (ANOVA) and a paired *t*-test. The effect of the blood volume correction on cbOEF-AI was also evaluated using a paired *t*-test. $P < 0.05$ was considered to indicate a significant difference.

RESULTS

Hemodynamic parameters calculated from all patients are given in Table 1. In one patient who had lesions of mild stenosis in the right ICA and severe stenosis in the left MCA, the side of severer stenotic lesion was defined as ipsilateral. All parameters were significantly affected by the stenoocclusive lesion in the ipsilateral hemisphere. Figure 1 shows representative images of qOEF, $cbOEF_{SS}$ and $cbOEF_{BO}$ calculated from a single patient's data. cbOEF images are presented without CBV correction. qOEF and cbOEF images were similar although cbOEF showed higher values in the sagittal sinus compared with qOEF. Since the qOEF image was calculated from $^{15}O_2$ and $C^{15}O_2$ data in the steady-state method, $cbOEF_{SS}$ and qOEF images are very similar, wheras values in the sagittal sinus of the $cbOEF_{SS}$

image was higher than that of $cbOEF_{BO}$.

The relationship between qOEF-AI and cbOEF-AI without CBV correction is presented in Figure 2. Both cbOEF-AIs ($cbOEF_{SS}$-AI and $cbOEF_{BO}$-AI) are linearly well correlated (R = 0.98 and 0.92, respectively) with qOEF-AI. However, $cbOEF_{SS}$-AI significantly underestimated the AI of OEF ($P < 0.05$; paired *t*-test), especially with a greater AI (y = 0.64x + 0.36) (Fig. 2A). The difference between $cbOEF_{BO}$-AI and qOEF-AI was not significant (y = 1.00x + 0.02) (Fig. 2B).

To remove the effect of radioactivity on the vascular blood volume, $cbOEF_C$ was calculated using the $C^{15}O$ image. Table 2 shows the slope, square of the correlation coefficient, bias and coefficient of variation obtained from the relationship between qOEF-AI and cbOEF-AI simulated by changing the contribution factor of α. The slope between qOEF-AI vs. $cbOEF_{SS}$-AI was improved by the CBV correction with the increase of α; however, that of qOEF-AI vs. $cbOEF_{BO}$-AI was apart from the line of identity with a greater α. Graphs in Figure 3 show the correlation coefficient and bias between qOEF-AI and cbOEF-AI as a function of α. The square of the correlation coefficient between qOEF-AI and $cbOEF_{SS}$-AI was maximum when α was close to 0.5 (Fig. 3A), although the mean bias continued to decrease up to $\alpha = 0.7$ (Fig. 3B) and increased with a greater α. The square of the correlation coefficient between qOEF-AI and $cbOEF_{BO}$-AI was maximum at $\alpha = 0$ (without CBV correction), and decreased with a greater α. The bias was gradually increased when α was greater than 0.5.

DISCUSSION

Evaluation of hemodynamic status is important in chronic atherothrombotic

ICA or MCA occlusive disease because patients with misery perfusion have a higher risk of stroke recurrence compared to patients with normal OEF (*2*,*5*,*6*). The ^{15}O-gas PET study is a useful method for evaluation of hemodynamic parameters and assessment of OEF to detect misery perfusion. The original method for evaluation of cerebral oxygen consumption was proposed by Jones et al. using the non-invasive steady-state method (*22*), and the concept of misery perfusion was reported by Baron et al. using the similar count-based method (1). This non-invasive method was modified and quantitative measurements were established for evaluation of hemodynamic parameters (*3*,*4*,*8*). However, these quantitative methods requires arterial blood sampling, which prevents its use in clinical studies because it takes a long time to evaluate one patient, including the arterial line procedure and other arrangements for the study. The noninvasive count-based method in the ^{15}O-gas PET study is a useful method without these problems, and can be made widely available in PET centers with an inhouse cyclotron. An advantage of this count-based method would be the possibility of efficient patient studies conducted more quickly and successfully without complicated procedures to yield quantitative metabolic data (*4*,*23*). However, this relative method has not been validated as to whether the AI of OEF can appropriately detect misery perfusion without CBV correction (*14*,*16*).

In the present study, both cbOEF-AIs showed a linear correlation against qOEF-AI, although cbOEF$_{SS}$-AI significantly underestimated qOEF-AI. The correlation coefficient was better in cbOEF$_{SS}$-AI than cbOEF$_{BO}$-AI. To improve the slope of correlation, blood volume correction for cbOEF was applied because qOEF was corrected for the effect of CBV. As observed in regional differences in hemodynamic parameters, CBV was significantly greater in the ipsilateral

hemisphere than in the contralateral hemisphere, and this difference was considered to affect cbOEF values. In $cbOEF_{SS}$-AI, the CBV correction using Eq. 1 improved the slope of the correlation and the correlation coefficient was better at $\alpha = 0.5$ compared with no CBV correction. On the other hand, $cbOEF_{BO}$-AI did not show any improvement in the slope nor mean bias with CBV correction. Derdeyn et al. assumed that the cbOEF image without CBV correction would enhance OEF-AI with a higher vascular radioactivity due to vasodilatation caused by a decrease in perfusion pressure in the compromised region (*14*). However, unexpectedly, $cbOEF_{SS}$-AI showed an underestimation of qOEF-AI and the slope of correlation was improved in the greater contribution factor of α with CBV correction, although α greater than 0.8 decreased in the correlation coefficient and increased bias. This underestimation might be caused by the greater influence of blood volume, or intravascular radioactivity, on the CO_2 image than on the O_2 image, although we did not evaluate which image was more influenced by changes in CBV in the present study. Thus, in the steady-state method, CBV correction with appropriate α (about 0.5 in our method) also combined with correction by the slope of correlation would provide better results than un-corrected $cbOEF_{SS}$-AI. On the other hand, $cbOEF_{BO}$-AI showed a fair correlation with qOEF-AI, and the correlation coefficient was maximum at $\alpha = 0$. This result means that cbOEF-AI can be used without CBV correction in the bolus method. In the image of $cbOEF_{BO}$, early arterial phase of dynamic data was eliminated to reduce influence of vascular radioactivity (19), which may have reduced the effects of blood volume on $cbOEF_{BO}$ image.

Grubb et al. tried to estimate the risk of recurrent stroke in patients with symptomatic carotid artery occlusion using cbOEF-AI (*5,14*). They applied the regional AI of OEF obtained from the $^{15}O_2/H_2{}^{15}O$ ratio using the bolus method after

normalization of the global cbOEF mean to get 0.40. Sensitivity and specificity between qOEF and cbOEF was similar in the analysis of receiver operating characteristics in the prediction of recurrent stroke (*14*). Ibaraki et al. reported the count-based method using lookup-tables for relative measurement of CBF, OEF, and $CMRO_2$ (16). For the calculation of the lookup-tables, CBF and OEF in the reference brain region were assumed to be 50.0 (mL/ min/ 100 mL) and 0.40, respectively. The constant CBV value of 4.0 (mL/ 100 mL) was used over the whole brain as well. They reported that the differences in CBV caused large errors in estimation of OEF and $CMRO_2$ in severe reduction of CBF and/or OEF. This result indicates difficulty in the method for analysis of severely impaired regions affected by ischemic CVD. We did not apply the global normalization method in calculation of cbOEF and observed excellent correlations when comparing qOEF-AI and cbOEF-AI, even without CBV correction. This simple method would be useful for clinical ^{15}O-PET studies, especially when using PET/CT machines which lead to difficulties in arterial sampling. Furthermore, $cbOEF_{BO}$-AI may not require the $C^{15}O$ scan for CBV correction if the method is used only for the diagnosis of regional misery perfusion.

The correlation coefficient was better in $cbOEF_{SS}$-AI than in $cbOEF_{BO}$-AI in the present study. This is because qOEF was calculated by the steady-state method and the image was based on the $^{15}O_2/C^{15}O_2$ image. If the qOEF image had been calculated by the bolus method, $cbOEF_{BO}$-AI may have shown better. Our method for $cbOEF_{BO}$-AI used images of bolus water injection and continuous $^{15}O_2$ inhalation, which was different from the original method studied by Derdeyn et al. (*14*). The results might be different between the two methods. However, the correlation between qOEF-AI and $cbOEF_{BO}$-AI was acceptable results even using the continuous

inhalation method for $^{15}O_2$ images. Five patients in the present study had misery perfusion determined by absolute OEF value (> 52.0 %) using data from healthy volunteers in our institute. All of them can be determined by the threshold of 1.18 and greater in qOEF-AI. A threshold of 1.12 with $cbOEF_{SS}$-AI is identical to that of qOEF-AI if the CBV correction is not applied (Fig. 2A). A threshold of 1.15 and greater in $cbOEF_{BO}$-AI provides one false positive and one false negative (Fig. 2B), and thus, the diagnostic accuracy was better in our results. However, the sample population was small and more patients should be needed to determine an appropriate threshold for clinical diagnosis.

A disadvantage of the count-based method would be a difficulty in the detection of global changes in OEF. Bilateral arterial lesions with severe stenoocclusive change may not be evaluated appropriately. However, most patients with bilateral stenotic lesions have fair cerebral circulation in the side of less severe stenosis in our experience. Quantitative measurement of CBF would be needed in cases of global hemodynamic impairment.

CONCLUSION

The feasibility of the count-based OEF method for detection of misery perfusion was evaluated with estimation of the CBV effect on OEF-AI calculation. Our method without global normalization for cbOEF successfully estimated OEF-AI in patients with misery perfusion. $cbOEF_{SS}$-AI obtained from the steady-state method would require CBV correction or correction for the underestimation of OEF-AI, while $cbOEF_{BO}$-AI would not need any correction. The cbOEF method would be useful in clinical studies for the evaluation of misery perfusion in ischemic CVD because it would reduce examination time and stress to patients.

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FIGURE LEGENDS

FIGURE 1.

Quantitative OEF (qOEF) and count-based OEF (cbOEF) images obtained from a single patient. ROIs placed on bilateral MCA territories are shown in the qOEF image (left). $cbOEF_{SS}$ (middle) was calculated from the division of $^{15}O_2$ and $C^{15}O_2$ images in the steady-state method and $cbOEF_{BO}$ (right) was calculated from $^{15}O_2$ and bolus $H_2{}^{15}O$-PET. cbOEF images are not corrected for the effect of intravascular radioactivity using the $C^{15}O$ image. Note high values in the sagittal sinus.

FIGURE 2.

Correlation of asymmetry indexes (AI) between qOEF (qOEF-AI) and cbOEF by $^{15}O_2/C^{15}O_2$ ($cbOEF_{SS}$-AI) (A) or $^{15}O_2/H_2{}^{15}O$ ($cbOEF_{BO}$-AI) (B) in all patients (n = 18). Both cbOEF-AIs are linearly well correlated. However, $cbOEF\text{-}AI_{SS}$ underestimated qOEF-AI significantly, especially with a greater AI ($P < 0.05$), while $cbOEF\text{-}AI_{BO}$ was not significantly different from qOEF-AI. Dashed line is a line of identity.

FIGURE 3.

Changes in the square of the correlation coefficient (A) and bias (B) calculated from plots between qOEF-AI vs. cbOEF-AI obtained by CBV correction with changes in the contribution factor of α. Bias is the mean of absolute distance between each plot and line of identity. The correlation coefficient between qOEF-AI and $cbOEF_{SS}$-AI (solid line) was maximum when α was close to 0.5 and the mean bias was minimum at $\alpha = 0.7$. On the other hand, correlation the coefficient in the relationship between qOEF-AI and $cbOEF_{BO}$-AI (dashed line) was maximum and the bias was minimum at $\alpha = 0$.

Table 1 Hemispheric differences in cerebrovascular diseases (n = 18)

	Ipsilateral	Contralateral	AI*	*P*†
CBF (mL/min/100 g)	32.7 ± 7.5	39.2 ± 5.9	0.84 ± 0.15	< 0.01
$CMRO_2$ (mL/min/100 g)	2.68 ± 0.42	3.02 ± 0.39	0.89 ± 0.11	< 0.01
OEF (%)	48.6 ± 11.7	44.5 ± 6.1	1.08 ± 0.14	< 0.05
CBV (mL/100 g)	4.59 ± 0.79	4.26 ± 0.74	1.09 ± 0.12	< 0.05

* Asymmetric index = [ipsilateral value] / [contralateral value]

† Statistical analysis using a paired *t*-test

Table 2 Correlations between qOEF-AI vs. cbOEF-AI

	qOEF-AI vs. $cbOEF_{SS}$-AI				qOEF-AI vs. $cbOEF_{BO}$-AI			
α	Slope*	r^2	Bias(%)†	CV	Slope*	r^2	Bias(%)†	CV
0	0.64	0.96	2.8	1.1	1.00	0.84	3.5	0.8
0.3	0.68	0.98	2.4	1.2	1.05	0.84	3.8	0.9
0.5	0.71	0.98	2.2	1.2	1.09	0.83	4.0	0.9
0.7	0.73	0.98	2.1	1.1	1.13	0.82	4.4	0.9
1.0	0.78	0.96	2.3	0.9	1.19	0.77	5.1	1.0
1.2	0.82	0.91	2.6	0.8	1.24	0.71	6.2	1.0
1.4	0.86	0.84	3.0	0.9	1.29	0.62	7.8	1.0
1.6	0.91	0.75	3.5	1.2	1.31	0.45	10.7	1.1

*Slope of regression line between qOEF-AI and cbOEF-AI

†Mean bias in plots between qOEF-AI and cbOEF-AI

AI: asymmetry index

qOEF: quantitative OEF

$cbOEF_{SS}$-AI, $cbOEF_{BO}$-AI: AI of count-based OEF calculated from the steady-state and bolus method, respectively

r^2: Square of the correlation coefficient

CV: Coefficient of variation

Figure 1

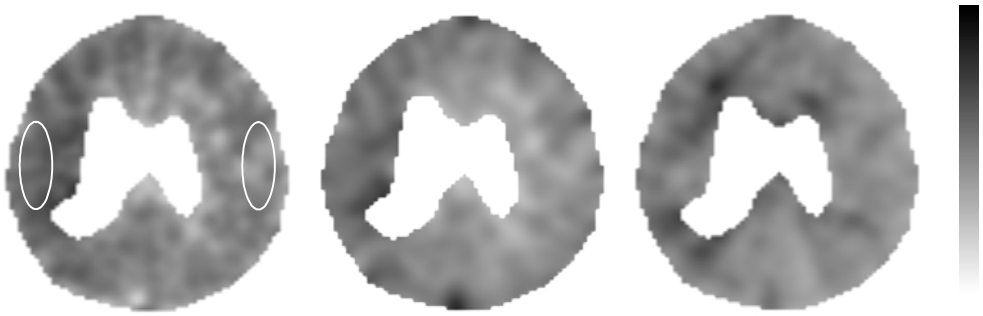

Figure 2

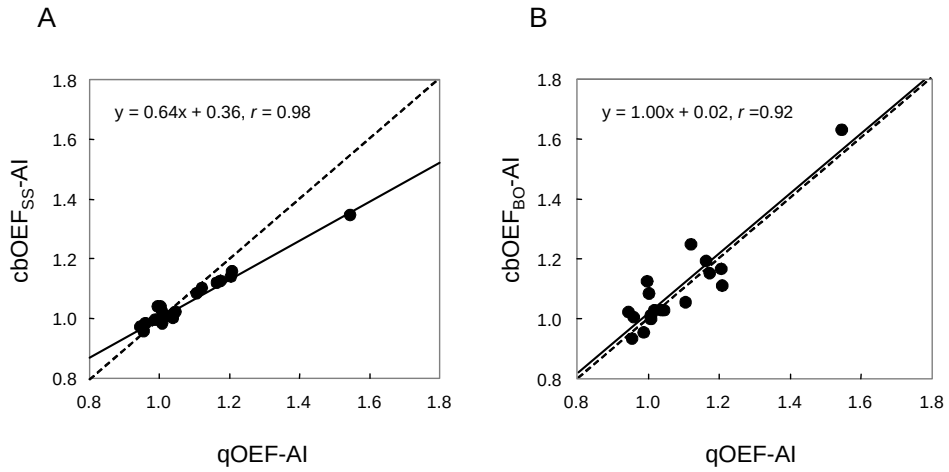

Figure 3