Diagnosis of Misery Perfusion Using Noninvasive ^{15}O-Gas PET

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To avoid arterial blood sampling and complicated analyses in ^{15}O-gas PET studies, we evaluated a noninvasive technique using the count-based method for measuring asymmetric increases in oxygen extraction fraction (OEF) in cerebrovascular disease. **Methods:** Eighteen patients (mean age ± SD, 61 ± 16 y) with atherothrombotic large-cerebral-artery 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 indices (AIs) were obtained (cbOEF$_{SS}$-AI and cbOEF$_{BO}$-AI, respectively) using regions of interest drawn bilaterally on the cerebral cortices. These AIs were compared with the AIs of absolute OEF (qOEF-AI) and with those after cerebral blood volume (CBV) correction. A contribution factor for this correction was defined as a 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 the 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 between qOEF-AI and cbOEF$_{BO}$-AI was adversely affected, and the mean bias was increased, with a greater α. **Conclusion:** cbOEF$_{BO}$-AI can fairly estimate the AI of OEF without CBV correction, whereas cbOEF$_{SS}$-AI might require CBV correction for better estimation. The examination time and stress to patients would be reduced with the count-based method because it is noninvasive.

Key Words: oxygen extraction fraction; misery perfusion; gas PET study; noninvasive method; cerebrovascular disease

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Measurement of the cerebral oxygen extraction fraction (OEF) with PET provides information on the hemodynamic status of patients with cerebrovascular disease. Misery perfusion, defined as an increase in OEF in the ischemic brain region (*1–7*), is caused by a decrease in cerebral blood flow, 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 are patients without misery perfusion (*2,5,6*), it is important to evaluate the hemodynamic status of those patients with atherothrombotic large-cerebral-artery 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 cerebral blood flow, OEF, and the cerebral metabolic rate of oxygen ($CMRO_2$) (*3,8*). Mintun et al. developed the 3-step method with 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 the PET examination. Establishing an arterial line before PET studies is invasive and time consuming and exposes the patient to unnecessary risks (*13*). For this reason, 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 OEF (cbOEF) method can detect misery perfusion correctly in the affected cerebral regions of patients with chronic cerebrovascular disease. The cbOEF method can noninvasively evaluate asymmetric increases of OEF with a simple calculation (*14–16*). However, the method for this semiquantitative 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 2 methods—continuous ^{15}O-gas inhalation and 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 cerebral blood volume (CBV) correction on cbOEF was also evaluated in both methods.

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MATERIALS AND METHODS

Subjects

The study consisted of 18 patients (16 men and 2 women; mean age ± SD, 61 ± 16 y) with ischemic cerebrovascular disease. Seventeen had occlusion (n = 8) or stenosis (n = 9, >70% diameter reduction) in the right or left internal carotid artery (n = 16) or in the middle cerebral artery (n = 1). The remaining patient had stenotic lesions in the right internal carotid artery and left middle cerebral artery. Six had experienced transient ischemic attacks, 10 had had a nondisabling hemispheric stroke with minor cerebral infarction shown on MRI, and 2 had no neurologic symptoms. The mean interval between the latest ischemic event and the individual PET scan was 3.4 ± 3.7 mo. The patients underwent MRI, MR angiography, or conventional angiography to examine all cerebral and arterial lesions. The percentage reduction in the diameter of stenotic lesions was measured by conventional angiography or ultrasonography for cervical lesions and by conventional angiography for intracranial lesions. The study was approved by the Ethical Committee of the University of Fukui, Faculty of Medical Sciences. Written informed consent was obtained from each subject before the study.

PET Procedures

All patients underwent PET with a whole-body tomography scanner (Advance; GE Healthcare), 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 4.6–5.7 mm in the transaxial direction and 4.0–5.3 mm in the axial direction. Transmission scanning 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 2-dimensional mode. The PET data were reconstructed using a Hanning filter with a resolution of 6.0 mm in 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 scanning was then started and continued for 5 min to calculate images of cerebral blood flow, OEF, and $CMRO_2$ (*3,8,18*). Each subject also inhaled $C^{15}O$ as a single dose of 1,000 MBq for CBV measurement (*18*). PET scanning was started at least 30 s after the tracer count had peaked in the brain and was continued for 3 min. Arterial blood was sampled 2 or 3 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 2 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 with a 3-min acquisition started at the time of bolus injection of the tracer (740 MBq). These data were used for calculation of the cbOEF image (*14,16*). To reduce the influence of intravascular radioactivity, we eliminated the initial frames (about 30 s) of dynamic PET data in the $H_2{}^{15}O$ bolus scan before count summation (*19*).

Absolute values of cerebral blood flow, CBV, OEF, and $CMRO_2$ were obtained from image calculation of the steady-state method (*3,8*). A cerebral-vessel–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 qOEF 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 $^{15}O_2$ scan was used in the calculation of the $CMRO_2$ image.

Data Analysis

Regional values were obtained from regions of interest (ROIs) drawn bilaterally on 3 slices of the cerebral cortex. Elliptic ROIs at 15 × 50 mm were placed bilaterally on cortical territories of the middle cerebral artery at the level of the centrum semiovale (Fig. 1). Before ROIs were placed, images of hemodynamic parameters and individual MR images were normalized anatomically for each subject using SPM2 (Wellcome Department of Cognitive Neurology). The ROIs placed in the ipsilateral hemisphere using normalized MR images were copied symmetrically at correspondent regions of the contralateral hemisphere in the standard brain space. In patients with cerebral infarction, the ROIs were placed so as to avoid the area of infarction on the normalized individual MR images. The same ROIs were applied to all parametric images of each subject. The values obtained from the ROIs were averaged for 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). 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 the CBV image, blood volume correction was considered necessary for cbOEF to correlate better with qOEF. To remove the influence of blood volume on regional values, we corrected the cbOEF using counts of the $C^{15}O$ image (Bq/g) with the following equations, which were modified and simplified from the method of CBV correction for absolute OEF of Lammertsma et al. (*8*):

$$cbOEF_C = \frac{cbOEF - \alpha \cdot X_{CO}}{1 - \alpha \cdot Xco} \qquad \text{Eq. 1}$$

$$X_{CO} = \frac{C_{CO_2}/S_{CO}}{C_{CO_2}/C_{CO}} \left[\text{or} \frac{C_{H_2O}/S_{CO}}{C_{H_2O}/C_{CO}} \right], \qquad \text{Eq. 2}$$

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

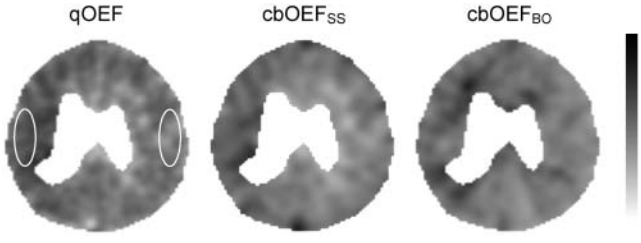

FIGURE 1. qOEF and cbOEF images obtained from a single patient. ROIs placed bilaterally on middle cerebral artery territories are shown in qOEF image. $cbOEF_{SS}$ was calculated from division of $^{15}O_2$ and $C^{15}O_2$ images in steady-state method, and $cbOEF_{BO}$ was calculated from $^{15}O_2$ and bolus $H_2{}^{15}O$ PET. cbOEF images are not corrected for effect of intravascular radioactivity using $C^{15}O$ image. Note high values in sagittal sinus.

TABLE 1
Hemispheric Differences in Cerebrovascular Diseases (n = 18)

Parameter	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

*By paired t test.
CBF = cerebral blood flow.

ROIs on the $C^{15}O$ image, and C_{CO2}, C_{H2O}, and C_{CO} are regional counts in the $C^{15}O_2$, $H_2{}^{15}O$, and $C^{15}O$ images, respectively. To determine S_{CO}, we drew 3 small, circular ROIs (5 mm in diameter) 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 an optimal value of α should exist 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 and $cbOEF_C$-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-measures 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 values of less than 0.05 were considered to indicate a significant difference.

RESULTS

Hemodynamic parameters calculated from all patients are given in Table 1. In 1 patient who had lesions of mild stenosis in the right internal carotid artery and severe stenosis in the left middle cerebral artery, the side of the more severe 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 than did qOEF. Because the qOEF images were calculated from $^{15}O_2$ and $C^{15}O_2$ data in the steady-state method, the $cbOEF_{SS}$ and qOEF images were similar, whereas values in the sagittal sinus were higher for $cbOEF_{SS}$ images than for $cbOEF_{BO}$ images.

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) linearly correlated well (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, we calculated $cbOEF_C$ 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 and $cbOEF_{SS}$-AI was improved by the CBV correction with an increase of α; however, that between qOEF-AI and $cbOEF_{BO}$-AI was farther from the line of identity with a greater α. The 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 maximal when α was close to 0.5 (Fig. 3A), although the mean bias continued to decrease up to an α of 0.7 (Fig. 3B) and increased with a greater α. The square of the correlation coefficient between qOEF-AI and $cbOEF_{BO}$-AI was maximal at an α of 0 (without CBV correction) and decreased with a greater α. The bias was gradually increased when α was greater than 0.5.

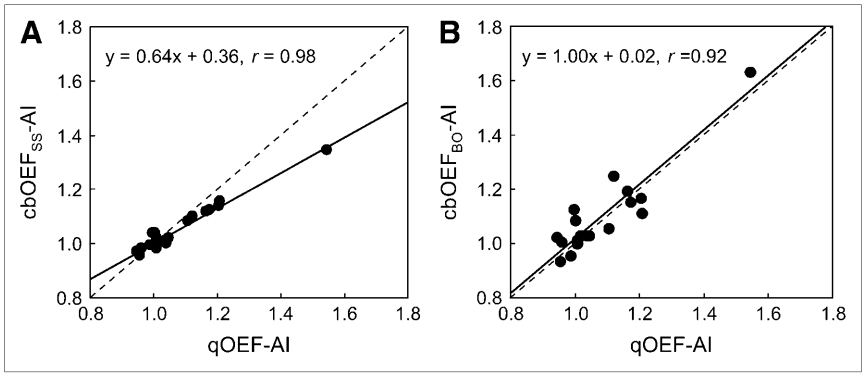

FIGURE 2. Correlation of qOEF-AI and $cbOEF_{SS}$-AI (A) or $cbOEF_{BO}$-AI (B) in all patients (n = 18). Both cbOEF-AIs are linearly well correlated. However, $cbOEF\text{-}AI_{SS}$ underestimated qOEF-AI significantly, especially with a greater AI ($P <$ 0.05), whereas $cbOEF\text{-}AI_{BO}$ was not significantly different from qOEF-AI. Dashed line is line of identity.

TABLE 2
Correlations Between qOEF-AI and 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.
CV = coefficient of variation.

DISCUSSION

Evaluation of hemodynamic status is important in chronic atherothrombotic internal-carotid-artery or middle-cerebral-artery occlusive disease because patients with misery perfusion have a higher risk of stroke recurrence than do patients with a normal OEF (*2,5,6*). ^{15}O-gas PET 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 noninvasive steady-state method (*22*), and the concept of misery perfusion was reported by Baron et al. using the similar count-based method (*1*). This noninvasive method was modified, and quantitative measurements were established for evaluation of hemodynamic parameters (*3,4,8*). However, these quantitative methods require arterial blood sampling, which prevents their use in clinical studies because of the lengthy time required to evaluate 1 patient, including the time to establish the arterial line and to make other arrangements for the study. The noninvasive count-based method in the ^{15}O-gas PET study is useful, lacks these problems, and can be made widely available in PET centers with an in-house cyclotron. An advantage of this count-based method would be the possibility of conducting patient studies efficiently, 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 in $cbOEF_{BO}$-AI. To improve the slope of the correlation, we corrected the blood volume for cbOEF 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 Equation 1 improved the slope of the correlation, and the correlation coefficient was better at an α of 0.5 than with no CBV correction. On the other hand, $cbOEF_{BO}$-AI showed no improvement in slope or 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 the correlation was improved by CBV correction with an appropriate contribution factor of α, although an α greater than 0.8 decreased 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 an appropriate α (about 0.5 in our method), combined with correction by the slope of correlation, would provide better results than would uncorrected $cbOEF_{SS}$-AI. On the other hand, $cbOEF_{BO}$-AI showed a fair correlation with qOEF-AI, and the correlation coefficient was maximal at an α of 0. This result means that cbOEF-AI can be used without CBV correction in the bolus method. In the image of $cbOEF_{BO}$, the early arterial phase of dynamic data was eliminated to reduce the influence of vascular radioactivity (*19*), which may have reduced the effects of blood volume on the $cbOEF_{BO}$ image.

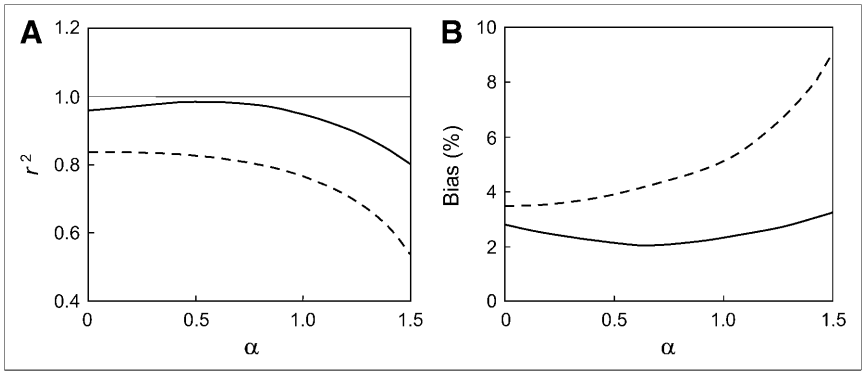

FIGURE 3. Changes in r^2 (A) and bias (B) calculated from plots of qOEF-AI vs. cbOEF-AI obtained by CBV correction with changes in contribution factor of α. Bias is mean of absolute distance between each plot and line of identity. Correlation coefficient between qOEF-AI and $cbOEF_{SS}$-AI (solid line) was maximal when α was close to 0.5, and mean bias was minimal when α was 0.7. In contrast, correlation coefficient in relationship between qOEF-AI and $cbOEF_{BO}$-AI (dashed line) was maximal and bias minimal when α was 0.

Grubb et al. (*5*) and Derdeyn et al. (*14*) tried to estimate the risk of recurrent stroke in patients with symptomatic carotid artery occlusion using cbOEF-AI. 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 were similar in the analysis of receiver operating characteristics in the prediction of recurrent stroke (*14*). Ibaraki et al. reported the count-based method using look-up tables for relative measurement of cerebral blood flow, OEF, and $CMRO_2$ (*16*). For the calculation of the look-up tables, cerebral blood flow 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. Ibaraki et al. reported that the differences in CBV caused large errors in estimations of OEF and $CMRO_2$ in cases of severe reduction of cerebral blood flow or OEF. This result indicates a difficulty with the method for analysis of severely impaired regions affected by ischemic cerebrovascular disease. 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 one is 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, 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 a better correlation. Unlike the original method studied by Derdeyn et al. (*14*), our method for $cbOEF_{BO}$-AI used images of bolus water injection and continuous $^{15}O_2$ inhalation. The results might be different between the 2 methods. However, the correlation between qOEF-AI and $cbOEF_{BO}$-AI was acceptable even with use of the continuous inhalation method for $^{15}O_2$ images. Five patients in the present study had misery perfusion as determined by an absolute OEF value (>52.0%) using data from healthy volunteers in our institute. Misery perfusion in all 5 of these patients can be determined by a threshold of 1.17 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 in $cbOEF_{BO}$-AI results in 1 false-positive and 1 false-negative (Fig. 2B), and thus, the diagnostic accuracy was fair in our results. However, the sample population was small, and more patients are 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 changes may not be evaluated appropriately. However, in our experience, most patients with bilateral stenotic lesions have fair cerebral circulation on the side with less severe stenosis. Quantitative measurement of cerebral blood flow would be needed in cases of global hemodynamic impairment.

CONCLUSION

The feasibility of the cbOEF 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, whereas $cbOEF_{BO}$-AI would not need any correction. The cbOEF method would be useful in clinical studies for the evaluation of misery perfusion in ischemic cerebrovascular disease because it would reduce examination time and stress to patients.

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Erratum

In the article "SPECT-Guided CT for Evaluating Foci of Increased Bone Metabolism Classified as Indeterminate on SPECT in Cancer Patients," by Römer et al. (*J Nucl Med.* 2006;47:1102–1106), Table 3 contains a transcriptional error introduced during correction of the page proofs. The data for scapula should be 0 benign and 2 indeterminate, instead of 1 benign and 0 indeterminate. We regret the error.