Shorter Examination Method for the Diagnosis of Misery Perfusion with Count-Based Oxygen Extraction Fraction Elevation in ^{15}O-Gas PET

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^{15}O-Gas PET is useful for evaluating hemodynamic status in patients with ischemic cerebrovascular disease. To reduce examination time and exposure to radioactive gas, we assessed a count-based method with shorter continuous $^{15}O_2$ gas inhalation. **Methods:** Twenty-five patients (66 ± 13 [mean ± SD] y old) with unilateral cerebrovascular stenoocclusive disease were examined by use of measurements of asymmetric oxygen extraction fraction (OEF) elevation. Dynamic PET scans of 1 min per frame were obtained starting 2 min after the beginning of $^{15}O_2$ inhalation at a constant flow rate (740 MBq/min). Each subject also underwent C^{15}O and H$_2$^{15}O PET with the bolus administration method. To evaluate the effects of different scan start times and durations during $^{15}O_2$ inhalation, we extracted and summed individual $^{15}O_2$ PET data from the dynamic $^{15}O_2$ dataset. Count-based OEF (cbOEF) images were calculated from $^{15}O_2$ and H$_2$^{15}O PET images. The asymmetric indices (AI) of cbOEF (cbOEF-AI) were obtained from regions of interest drawn on territories of the bilateral middle cerebral artery. These AI were compared with the AI of quantitative OEF (qOEF-AI). **Results:** The slopes of the regression lines and the coefficients of correlation between qOEF-AI and cbOEF-AI were close to 1.00 and greater than 0.79, respectively, regardless of different scan start times and durations. The cbOEF-AI obtained with a longer scan duration were closer to the qOEF-AI than those obtained with a shorter scan duration. Longer scan durations also provided better coefficients of correlation between cbOEF-AI and qOEF-AI regardless of scan start times. The coefficients of correlation between cbOEF-AI and qOEF-AI were greater than 0.90, except for cbOEF-AI obtained from $^{15}O_2$ images at 2–3 min after $^{15}O_2$ inhalation. **Conclusion:** The cbOEF obtained by $^{15}O_2$ imaging from 4 min after $^{15}O_2$ inhalation to 7 min or longer can correctly diagnose misery perfusion. The less invasive count-based PET method used in this study will be able to reduce examination time, exposure time, and stress for patients with ischemic cerebrovascular disease.

Oxygen-15-gas brain PET is the most reliable examination technique for evaluating misery perfusion, defined as impaired hemodynamics with a regional increase in the oxygen extraction fraction (OEF), in imaging modalities. Patients with this condition have a higher risk of stroke recurrence than patients with normal OEF (*1–4*). Several PET methods have been developed and used to calculate quantitative OEF (qOEF) for the diagnosis of misery perfusion (*5–9*). However, these methods require arterial blood sampling during the PET examination, which necessitates a long examination time and introduces the risk of bleeding from the arterial line.

Count-based OEF (cbOEF) methods can noninvasively evaluate asymmetric increases in OEF with a simple calculation as a substitution for qOEF measurements (*3,10–13*). In a previous study, we evaluated whether the asymmetry index (AI) of cbOEF (cbOEF-AI) could appropriately detect misery perfusion (*13*). The cbOEF-AI obtained with continuous $^{15}O_2$ gas inhalation and bolus H$_2$^{15}O injection could correctly estimate the AI of qOEF (qOEF-AI) without a C^{15}O image for cerebral blood volume (CBV) correction, whereas the cbOEF-AI obtained with continuous inhalation of $^{15}O_2$ and C$^{15}O_2$ required CBV correction (*13*). Although the former method can reduce the examination time for C$^{15}O_2$ scans, the cbOEF method with continuous $^{15}O_2$ inhalation still requires a long examination time to achieve an equilibrium of cerebral radioactivity.

The purposes of this study were to reduce examination time and to assess whether a new method with shorter continuous $^{15}O_2$ inhalation can appropriately evaluate misery perfusion. For these purposes, dynamic PET data acquisition was started before the steady state was reached during continuous $^{15}O_2$ inhalation. The appropriate examination time

for the use of the cbOEF method to evaluate side-by-side OEF differences in cerebrovascular diseases was estimated.

MATERIALS AND METHODS

Subjects

The subjects were 25 patients (15 men and 10 women; age [mean $\pm$ SD], 66 $\pm$ 13 y) with unilateral cerebrovascular stenoocclusive disease. The patients had occlusion ($n = 9$) or stenosis ($n = 16$; diameter reduction >70%) of the unilateral internal carotid artery ($n = 20$) or the middle cerebral artery (MCA) ($n = 3$). Because the remaining 2 patients had unilateral arterial occlusion and mild stenosis (<70%) of the contralateral side, that is, right MCA occlusion with mild left MCA stenosis and left internal carotid artery occlusion with mild right internal carotid artery stenosis, the side of the arterial occlusion was defined as the ipsilateral side. Seven patients had experienced transient ischemic attacks; 10 had experienced a nondisabling hemispheric stroke with minor cerebral infarctions, as shown on MRI; and 8 had no neurologic symptoms. 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 scans were acquired in the 2-dimensional mode with a whole-body tomography scanner (Advance; GE Healthcare), which permits the simultaneous acquisition of 35 image slices with an interslice spacing of 4.25 mm (14). Performance tests showed the intrinsic resolutions of the scanner to be 4.6–5.7 mm in the transaxial direction and 4.0–5.3 mm in the axial direction. We obtained a blank scan before beginning the PET examination with the ^{68}Ge/^{68}Ga line source. Patients were positioned on the scanner bed with their heads immobilized with a head holder.

Figure 1 shows the timing of PET examinations in the present study. Before tracer administration, a small cannula was placed in the right brachial artery for blood sampling, and a transmission scan was obtained for 10 min in each subject for attenuation
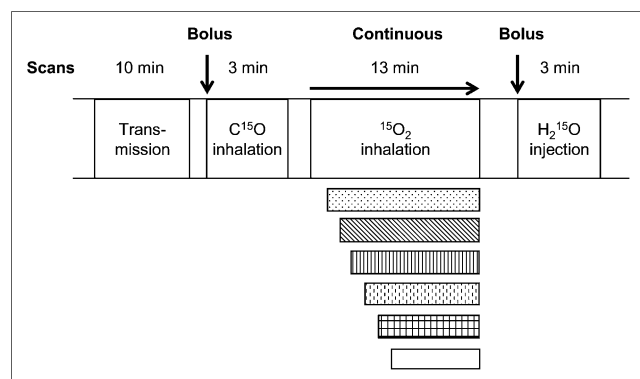

FIGURE 1. Scan protocol and data preparation for ^{15}O-gas PET. For cbOEF calculation, subsets of ^{15}O$_2$ dynamic data were extracted at 2, 3, 4, 5, 6, and 7 min (bars below diagram, from top to bottom, respectively) after beginning of ^{15}O$_2$ inhalation up to 13 min. cbOEF-AI was calculated from ^{15}O$_2$ images and H$_2$^{15}O PET scans for 3 min. qOEF was calculated from ^{15}O$_2$ images obtained from 8 min to 13 min after ^{15}O$_2$ inhalation and H$_2$^{15}O images with arterial blood data. C^{15}O data were used for CBV correction of qOEF.

correction. For ^{15}O-gas PET scans, a nasal tube was placed in the nose of patients, and an oxygen mask was used to cover the nose and the mouth. ^{15}O-Gas was administered from the tube, and radioactive gas in the expired air was vacuumed from the mask. Subjects inhaled C^{15}O$_2$ as a single dose of 1,000 MBq for CBV measurements (14). PET was started at least 30 s after the tracer count had peaked in the brain and was continued for 3 min. Continuous ^{15}O$_2$ inhalation was started at a constant flow rate of 740 MBq/min. Dynamic PET scans of 1 min per frame were obtained for 11 min starting 2 min after the beginning of continuous ^{15}O$_2$ inhalation. Next, bolus H$_2$^{15}O scans were obtained with a 3-min acquisition starting at the time of bolus injection of the tracer at 740 MBq. Arterial blood was sampled, and radioactivity in the blood samples was immediately measured with a scintillation counter to determine arterial blood activity (13,14). Reconstructions of PET data were performed by use of filtered backprojection with a Hanning filter at a cutoff of 6.0 mm full width at half maximum in the transaxial direction.

Parametric images of cerebral blood flow, CBV, OEF, and cerebral metabolic rate for oxygen were calculated from PET images and arterial blood data (5,7,14). In the count-based method, individual ^{15}O$_2$ data were extracted from the original dynamic ^{15}O$_2$ dataset and summed to simulate different acquisition start times and scan durations during ^{15}O$_2$ inhalation (Fig. 1). cbOEF images were calculated from ratios of ^{15}O$_2$ and H$_2$^{15}O images by use of ^{15}O$_2$ images variously extracted from the dynamic PET data (Table 2).

Data Analysis

Regional values were obtained from regions of interest (ROIs) drawn bilaterally on 3 slices of the cerebral cortex as reported previously (13). In brief, elliptic ROIs of 15 × 50 mm were placed bilaterally on cortical territories of the MCA at the 3 slice levels of the centrum semiovale. Before the ROIs were placed, each image of hemodynamic parameters was normalized anatomically with SPM2 (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, U.K.). The ROIs placed in the ipsilateral hemisphere of normalized MR images were copied symmetrically at corresponding regions in the contralateral hemisphere. The same ROIs were applied to all parametric images for each subject. The values obtained from the ROIs in each hemisphere were averaged.

The cbOEF-AI was compared with the qOEF-AI, which was obtained from ^{15}O$_2$ images summed for 8–13 min after ^{15}O$_2$ inhalation. The slopes of the regression lines and the coefficients of correlation (r) between cbOEF-AI and qOEF-AI were calculated, and the mean distance of all plots from the line of identity (bias) was determined. The cbOEF-AI was applied to the diagnosis of misery perfusion on the basis of absolute OEF values (>52.0%) obtained from healthy volunteers at the University of Fukui (13,14). The threshold of 1.15 for cbOEF-AI, which was equivalent to that of 1.17 for qOEF-AI in our previous study (13), was applied to the cbOEF method in the present study. Differences between the 2 hemispheres for each hemodynamic parameter were compared statistically by use of repeated-measures analysis of variance and a paired t test. P values of less than 0.05 were considered to indicate a significant difference.

RESULTS

Regional parametric values for each hemisphere in all patients are presented in Table 1. All parameters except for CBV were affected by stenoocclusive lesions in the ipsi-

TABLE 1
Hemispheric Differences in Cerebrovascular Diseases ($n = 25$)

Parameter	Value for:		AI	P*
	Ipsilateral hemisphere	Contralateral hemisphere		
Cerebral blood flow (mL/min/100 g)	31.8 ± 4.94	34.7 ± 5.96	0.92 ± 0.09	<0.01
Cerebral metabolic rate for oxygen (mL/min/100 g)	2.21 ± 0.37	2.35 ± 0.42	0.94 ± 0.10	<0.01
OEF (%)	44.4 ± 6.0	43.3 ± 4.8	1.02 ± 0.06	<0.05
CBV (mL/100 g)	3.23 ± 0.88	3.18 ± 0.58	1.00 ± 0.13	0.30

*As determined with paired t test.

lateral hemisphere. Table 2 shows the slope, r, and bias obtained from the relationship between qOEF-AI and cbOEF-AI. The slopes of the regression lines were close to approximately 1.00, and the correlations between qOEF-AI and cbOEF-AI were greater than 0.79, although both acquisition start times and durations were different. Longer acquisition times showed a better correlation and smaller bias in the relationship between cbOEF-AI and qOEF-AI, irrespective of the acquisition start times for $^{15}O_2$ images. Figure 2 shows changes in cbOEF-AI at each $^{15}O_2$ acquisition start time and duration in 3 patients with misery perfusion. Continuous $^{15}O_2$ inhalation required at least 7 min to detect misery perfusion at a threshold of 1.15 for cbOEF-AI, even though the acquisition start times were varied.

DISCUSSION

The cbOEF method could identify patients with misery perfusion, even when $^{15}O_2$ images were acquired before an equilibrium of blood and brain radioactivities was reached. The major advantage of the cbOEF method is that it is a simpler and quicker method of PET examination than the conventional qOEF method, which requires arterial blood sampling and complicated data analysis. Patients with cerebrovascular diseases in Japan have usually been examined with quantitative methods, such as the steady-state method for ^{15}O-gas tracers (15). Although cbOEF methods that make use of bolus tracer administration to estimate the regional AI of OEF have been developed (10–12), we applied continuous $^{15}O_2$ inhalation and a bolus $H_2^{15}O$ injection to calculate the cbOEF in the present study (13). This cbOEF-AI method does not need a $C^{15}O$ image for CBV correction, and the results obtained with this method showed good correlations between qOEF-AI and cbOEF-AI. However, a long waiting time for achieving equilibrium during continuous $^{15}O_2$ inhalation was required. A shorter examination time for this method was evaluated in the present study by use of dynamic $^{15}O_2$ data acquisition started before the steady state was reached. The $^{15}O_2$ images were acquired from 2 min after the start of continuous $^{15}O_2$ inhalation because the level of radioactivity in the brain was not high enough at an inhalation time of less than 2 min.

As shown in Table 2, even when brief $^{15}O_2$ inhalation was applied to the cbOEF method, cbOEF-AI showed good linearity with qOEF-AI. The correlations between cbOEF-AI and qOEF-AI were greater than 0.90, except for $^{15}O_2$ imaging at 2–3 min after $^{15}O_2$ inhalation. This very early and short scan timing resulted in high levels of noise in the

TABLE 2
Correlations Between qOEF-AI and cbOEF-AI for Different Acquisition Start Times and Scan Durations ($n = 25$)

Scan duration (min)	Acquisition start time																	
	2 min			3 min			4 min			5 min			6 min			7 min		
	Slope	r	Bias	Slope	r	Bias	Slope	r	Bias	Slope	r	Bias	Slope	r	Bias	Slope	r	Bias
1	0.73	0.79	2.5	1.14	0.92	2.7	1.14	0.95	2.0	0.86	0.93	1.7	0.81	0.90	1.9	0.81	0.94	1.8
2	0.98	0.93	2.1	1.09	0.96	1.7	1.05	0.96	1.5	0.84	0.96	1.2	0.81	0.94	1.7	0.93	0.96	1.4
3	1.00	0.95	1.6	0.94	0.95	1.6	0.93	0.97	1.2	0.83	0.96	1.2	0.90	0.97	1.3	0.92	0.96	1.3
4	0.90	0.94	1.5	0.89	0.96	1.2	0.89	0.97	1.0	0.92	0.98	1.0	0.91	0.97	1.2	0.95	0.98	1.0
5	0.87	0.96	1.3	0.89	0.97	1.0	0.91	0.98	1.0	0.93	0.98	1.0	0.93	0.98	0.8	0.95	0.98	0.7
6	0.86	0.97	1.1	0.92	0.98	0.9	0.92	0.98	1.0	0.98	0.99	0.7	0.94	0.98	0.8	1.01	0.98	0.8
7	0.89	0.98	1.0	0.92	0.98	0.9	0.96	0.99	0.7	0.99	0.99	0.7	0.99	0.99	0.7			
8	0.90	0.99	0.8	0.94	0.99	0.7	0.95	0.99	0.7	1.04	0.99	0.8						
9	0.91	0.99	0.7	0.94	0.99	0.6	1.00	0.99	0.6									
10	0.91	0.99	0.6	0.97	0.99	0.6												
11	0.95	0.99	0.6															

Scan duration was time after beginning of $^{15}O_2$ image scanning. Slope represents slope of regression line between qOEF-AI and cbOEF-AI. Bias represents mean distance between line of identity and plots of qOEF-AI and cbOEF-AI (%).
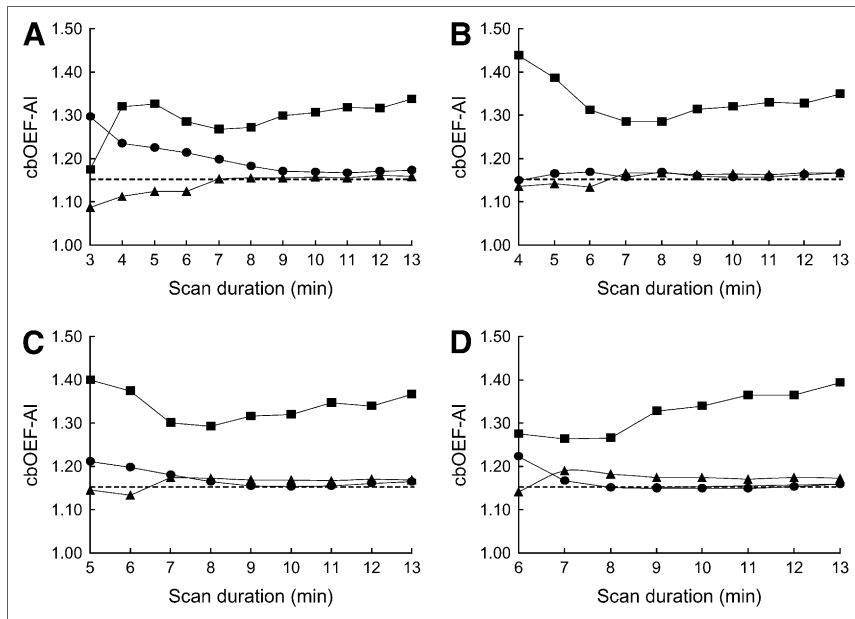
FIGURE 2. Changes in cbOEF-AI for 3 patients with misery perfusion, as determined from $^{15}O_2$ images with various scan durations started at 2 min (A), 3 min (B), 4 min (C), and 5 min (D) after beginning of $^{15}O_2$ inhalation. Misery perfusion was defined in our previous study as increase in qOEF of 52.0% or greater, which is equivalent to threshold of 1.17 for qOEF-AI (qOEF-AI = 1.17 for ● and ▲ and 1.36 for ■). Threshold of 1.15 for cbOEF-AI in present study (dashed line) was equivalent to threshold of 1.17 for qOEF-AI in our previous study. Regardless of different acquisition start times, continuous $^{15}O_2$ inhalation for 7 min or longer would be required to correctly detect misery perfusion.

$^{15}O_2$ images, and quality was poor. Longer scan durations also yielded better correlations and smaller biases between qOEF-AI and cbOEF-AI, despite different acquisition start times.

Three of 25 patients had significantly higher OEF in the ipsilateral hemisphere. $^{15}O_2$ inhalation times of 7 min or longer should be used to diagnose misery perfusion with the cbOEF method, although the sample population of patients with misery perfusion in the present study may have been small (Fig. 2). To minimize the PET examination time, $^{15}O_2$ images summed from 4 to 7 min would be appropriate, because they provided the maximal r value (0.97) (Table 2). Therefore, this cbOEF method could reduce $^{15}O_2$ inhalation time to about half that in the steady-state method. The total examination time should be 30 min or less with this method when CBV correction of OEF is not used.

Cerebral vascular volume is usually increased in the impaired circulation and is considered to affect cbOEF values. However, in our previous study, CBV correction did not improve the accuracy of estimation of the AI of OEF with the bolus ^{15}O-water injection method, whereas estimation with continuous $C^{15}O_2$ inhalation required CBV correction for a better correlation (*13*). This is why we used the former method without CBV correction. A simple ^{15}O-gas PET method would be promising for the evaluation of cerebral hemodynamics, especially with a PET/CT scanner, which can lead to difficulties in arterial sampling because of its deep gantry. The use of new scanners, such as PET/CT and PET/MRI scanners, would be useful for motion correction during and between scans because precise attenuation correction would be beneficial for the cbOEF method, which compares the left-to-right asymmetric changes. On the other hand, in the application of ^{15}O-gas methods for 3-dimensional-mode scanners (as opposed to 2-dimensional-mode scanners), random and scattered coincidences from high levels of radioactivity in the nasal cavity and the body should be carefully corrected.

CONCLUSION

For cbOEF-AI with continuous $^{15}O_2$ inhalation, PET acquisition from 4 to 7 min after the start of $^{15}O_2$ inhalation provided an appropriate estimation of qOEF-AI even before an equilibrium of radioactivity was reached and could properly diagnose patients with misery perfusion. The cbOEF method described here can considerably reduce examination time, exposure time, and stress for patients compared with conventional methods.

REFERENCES

1. Baron JC, Bousser MG, Rey A, et al. Reversal of focal "misery-perfusion syndrome" by extra-intracranial arterial bypass in hemodynamic cerebral ischemia: a case study with ^{15}O positron emission tomography. *Stroke.* 1981;12: 454–459.
2. Yamauchi H, Fukuyama H, Nagahama Y, et al. Evidence of misery perfusion and risk for recurrent stroke in major cerebral arterial occlusive diseases from PET. *J Neurol Neurosurg Psychiatry.* 1996;61:18–25.
3. Grubb RL Jr, Derdeyn CP, Fritsch SM, et al. Importance of hemodynamic factors in the prognosis of symptomatic carotid occlusion. *JAMA.* 1998;280:1055–1060.

4. Yamauchi H, Fukuyama H, Nagahama Y, et al. Significance of increased oxygen extraction fraction in five-year prognosis of major cerebral arterial occlusive diseases. *J Nucl Med.* 1999;40:1992–1998.

5. Frackowiak RS, Lenzi GL, Jones T, et al. Quantitative measurement of regional cerebral blood flow and oxygen metabolism in man using ^{15}O and positron emission tomography: theory, procedure, and normal values. *J Comput Assist Tomogr.* 1980;4:727–736.

6. Mintun MA, Raichle ME, Martin WR, Herscovitch P. Brain oxygen utilization measured with O-15 radiotracers and positron emission tomography. *J Nucl Med.* 1984;25:177–187.

7. Lammertsma AA, Wise RJ, Heather JD, et al. Correction for the presence of intravascular oxygen-15 in the steady-state technique for measuring regional oxygen extraction ratio in the brain, 2. Results in normal subjects and brain tumor and stroke patients. *J Cereb Blood Flow Metab.* 1983;3:425–431.

8. Senda M, Buxton RB, Alpert NM, et al. The ^{15}O steady-state method: correction for variation in arterial concentration. *J Cereb Blood Flow Metab.* 1988;8:681–690.

9. Sadato N, Yonekura Y, Senda M, et al. PET and the autoradiographic method with continuous inhalation of oxygen-15-gas: theoretical analysis and comparison with conventional steady-state methods. *J Nucl Med.* 1993;34:1672–1680.

10. Derdeyn CP, Videen TO, Simmons NR, et al. Count-based PET method for predicting ischemic stroke in patients with symptomatic carotid arterial occlusion. *Radiology.* 1999;212:499–506.

11. Derdeyn CP, Videen TO, Grubb RL Jr, Powers WJ. Comparison of PET oxygen extraction fraction methods for the prediction of stroke risk. *J Nucl Med.* 2001;42:1195–1197.

12. Ibaraki M, Shimosegawa E, Miura S, et al. PET measurements of CBF, OEF, and CMRO$_2$ without arterial sampling in hyperacute ischemic stroke: method and error analysis. *Ann Nucl Med.* 2004;18:35–44.

13. Kobayashi M, Okazawa H, Tsuchida T, Kawai K, Fujibayashi Y, Yonekura Y. Diagnosis of misery perfusion using noninvasive ^{15}O-gas PET. *J Nucl Med.* 2006;47:1581–1586.

14. Okazawa H, Yamauchi H, Sugimoto K, et al. Quantitative comparison of the bolus and steady-state methods for measurement of cerebral perfusion and oxygen metabolism: positron emission tomography study using ^{15}O-gas and water. *J Cereb Blood Flow Metab.* 2001;21:793–803.

15. Ito H, Kanno I, Kato C, et al. Database of normal human cerebral blood flow, cerebral blood volume, cerebral oxygen extraction fraction and cerebral metabolic rate of oxygen measured by positron emission tomography with ^{15}O-labelled carbon dioxide or water, carbon monoxide and oxygen: a multicenter study in Japan. *Eur J Nucl Med Mol Imaging.* 2004;31:635–643.