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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Key Words: ischemic cerebrovascular disease; misery perfusion; oxygen extraction fraction; $^{15}$O-gas PET

DOI: 10.2967/jnumed.107.047118

$^{15}$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 time and exposure to radioactive gas, we assessed a count-based method with shorter continuous $^{15}$O$_2$ gas inhalation time and exposure to radioactive gas, we assessed a count-based method with shorter continuous $^{15}$O$_2$ gas inhalation time and exposure to radioactive gas, we assessed a count-based method with shorter continuous $^{15}$O$_2$ gas inhalation time and exposure to radioactive gas, we assessed a count-based method with shorter continuous $^{15}$O$_2$ gas inhalation time and exposure to radioactive gas, we assessed a count-based method with shorter continuous $^{15}$O$_2$ gas inhalation time and exposure to radioactive gas, we assessed a count-based method with shorter continuous $^{15}$O$_2$ gas inhalation time and exposure to radioactive gas, we assessed a count-based method with shorter continuous $^{15}$O$_2$ gas inhalation time and exposure to radioactive gas, we assessed a count-based method with shorter continuous $^{15}$O$_2$ gas inhalation time and exposure to radioactive gas.

Methods: Twenty-five patients (66 ± 13 [mean ± SD] y old) with unilateral cerebrovascular stenooocclusive 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 $^{13}$C$_2$O image for cerebral blood volume (CBV) correction, whereas the cbOEF-AI obtained with continuous inhalation of $^{15}$O$_2$ and $^{15}$O$_2$ required CBV correction (13). Although the former method can reduce the examination time for $^{15}$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 ± SD], 66 ± 13 y) with unilateral cerebrovascular stenooocclusive 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 (I-4). 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 in the transaxial direction and 4.0–5.3 mm in the axial direction. The subjects were 25 patients (15 men and 10 women; age [mean ± SD], 66 ± 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.

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**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-

![Figure 1](image-url)
TABLE 1
Hemispheric Differences in Cerebrovascular Diseases (n = 25)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ipsilateral hemisphere</th>
<th>Contralateral hemisphere</th>
<th>Al</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral blood flow (mL/min/100 g)</td>
<td>31.8 ± 4.94</td>
<td>34.7 ± 5.96</td>
<td>0.92 ± 0.09</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cerebral metabolic rate for oxygen (mL/min/100 g)</td>
<td>2.21 ± 0.37</td>
<td>2.35 ± 0.42</td>
<td>0.94 ± 0.10</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>OEF (%)</td>
<td>44.4 ± 6.0</td>
<td>43.3 ± 4.8</td>
<td>1.02 ± 0.06</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CBV (mL/100 g)</td>
<td>3.23 ± 0.88</td>
<td>3.18 ± 0.58</td>
<td>1.00 ± 0.13</td>
<td>0.30</td>
</tr>
</tbody>
</table>

*As determined with paired t test.

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

<table>
<thead>
<tr>
<th>Scan duration (min)</th>
<th>2 min</th>
<th>3 min</th>
<th>4 min</th>
<th>5 min</th>
<th>6 min</th>
<th>7 min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Slope</td>
<td>r</td>
<td>Bias</td>
<td>Slope</td>
<td>r</td>
<td>Bias</td>
</tr>
<tr>
<td>1</td>
<td>0.73</td>
<td>0.79</td>
<td>2.5</td>
<td>1.14</td>
<td>0.92</td>
<td>2.7</td>
</tr>
<tr>
<td>2</td>
<td>0.98</td>
<td>0.93</td>
<td>2.1</td>
<td>1.09</td>
<td>0.96</td>
<td>1.7</td>
</tr>
<tr>
<td>3</td>
<td>1.00</td>
<td>0.95</td>
<td>1.6</td>
<td>0.94</td>
<td>0.95</td>
<td>1.6</td>
</tr>
<tr>
<td>4</td>
<td>0.90</td>
<td>0.94</td>
<td>1.5</td>
<td>0.89</td>
<td>0.96</td>
<td>1.2</td>
</tr>
<tr>
<td>5</td>
<td>0.87</td>
<td>0.96</td>
<td>1.3</td>
<td>0.89</td>
<td>0.97</td>
<td>1.0</td>
</tr>
<tr>
<td>6</td>
<td>0.86</td>
<td>0.97</td>
<td>1.1</td>
<td>0.92</td>
<td>0.98</td>
<td>0.9</td>
</tr>
<tr>
<td>7</td>
<td>0.89</td>
<td>0.98</td>
<td>1.0</td>
<td>0.92</td>
<td>0.98</td>
<td>0.9</td>
</tr>
<tr>
<td>8</td>
<td>0.90</td>
<td>0.99</td>
<td>0.8</td>
<td>0.94</td>
<td>0.99</td>
<td>0.7</td>
</tr>
<tr>
<td>9</td>
<td>0.91</td>
<td>0.99</td>
<td>0.7</td>
<td>0.94</td>
<td>0.99</td>
<td>0.6</td>
</tr>
<tr>
<td>10</td>
<td>0.91</td>
<td>0.99</td>
<td>0.6</td>
<td>0.97</td>
<td>0.99</td>
<td>0.6</td>
</tr>
<tr>
<td>11</td>
<td>0.95</td>
<td>0.99</td>
<td>0.6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Scan duration was time after beginning of 15O2 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 (%).
$^{15}$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, 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.

ACKNOWLEDGMENTS

The authors thank Shingo Kasamatsu, Katsuya Sugimoto, Tetsuya Mori, and other staff of the Biomedical Imaging Research Center, University of Fukui, for their technical and clinical support. This study was partly funded by Grants-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (17209040, 18591334, and 19790861) and by the 21st Century COE Program (Medical Science).

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Published online: January 16, 2008.
Doi: 10.2967/jnumed.107.047118

This article and updated information are available at: http://jnm.snmjournals.org/content/early/2008/01/16/jnumed.107.047118.citation

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