The 15O continuous-inhalation method: Correction for intravascular signal using C15O

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Abstract. Cerebral oxygen metabolism (CMRO2) and fractional extraction (OEF) regional values obtained using the 15O steady-state method and positron-emission tomography (PET) were corrected for the activity remaining in blood vessels (a source of overestimation of the OEF neglected in the simple steady-state model) using an additional scan during continuous inhalation of nontoxic amounts of carbon monoxide labeled with 15O (C15O). The method was applied to ten serial PET studies. In normal tissue, OEF overestimation was 11% ± 2.6% and 9% ± 2.0% in gray and white matter, respectively. In pathological tissue, the OEF overestimation was, on average, higher than in normal tissue (28% ± 17% in the core of lesions), but more variable. In both normal and abnormal tissue, however, it was found that (1) the lower the real OEF, the larger the correction applied, and (2) the correction appears to be particularly necessary in situations of abnormally low OEF. The use of C15O continuous inhalation is a simple, direct, and accurate method for blood-activity correction when the 15O steady-state technique is employed to study pathophysiology.

Key words: Oxygen 15 steady state method – Position emission tomography – 15O labeled carbon monoxide – oxygen extraction fraction (OEF)

The 15O steady-state positron-emission-tomography (PET) technique (Jones et al. 1976) for studying both regional cerebral blood flow (rCBF) and oxygen metabolism (rCMRO2) has been widely applied to normal subjects (Frackowiak et al. 1980; Lebrun-Grandié et al. 1983) and pathological states (Ackerman et al. 1981; Baron et al. 1983; Frackowiak and Wise 1983). However, the basic form of this model (as commonly applied in clinical studies) has several theoretical limitations (Lammertsma et al. 1981). The main source of error affects the measurement of the oxygen extraction fraction (OEF) and consequently that of the CMRO2, and is due to the presence of unextracted 15O activity in the cerebral vascular spaces. If not corrected for, the OEF values obtained are systematically overestimated (Lebrun-Grandié et al. 1983; Lammertsma et al. 1981; Baron et al. 1981). A method of correcting for this error by measuring cerebral blood volume (CBV) using inhaled 11C-labeled carbon monoxide has recently been described (Lammertsma and Jones 1983), and the results of its application to a series of patients have been reported (Lammertsma et al. 1983).

However, the use of 15O-labeled carbon monoxide (C15O) for measuring intravascular activity should allow a more accurate and direct OEF correction because, as emphasized by Lammertsma and Jones (1983), the same positron emitter and the same principle (i.e., steady-state technique) are used in both 15O2 and C15O scans. Hence, the corrected OEF values are computed directly, i.e., without the first calculating the of uncorrected values.

The major hindrance to the use of C15O is the toxicity of carrier CO. Since we have succeeded in producing C15O in nontoxic amounts in our center, we decided to apply this simple method and the preliminary results are reported here.

Patients and methods

Production of C15O

The C15O was produced in a continuous flow. A mixture of 0.25% O2 in N2 was used as the combined target and sweep gas, the target pressure being two atmospheres above atmospheric pressure. Bombardment was performed using a 20-μA/8-MeV deuteron beam degraded to 6.5 MeV by the entrance foil of the target.

The product of the 14N (d, n) 15O reaction was 15O2; this was then converted to C15O by activated charcoal at 900°C, which also removed the impurities. After furnacing, the traces of C15O2 produced by the reaction (about 5%) were removed by a soda line trap.

The gas was piped to the positron tomograph at a CO concentration of 0.4%, a flow rate of 500 ml/min (maximal concentration of stable CO inhaled, ~ 0.03%), and a specific activity of 0.03 mCi/ml.

Procedure

The PET procedure included (1) a 68Ge-68Ga transmission scan for the correction of photon attenuation and (2) three serial emission scans, during the inhalation of C15O2, 15O2, and C15O at three head levels, i.e., 2.4, and 6 cm above the orbitomeatal line, respectively. Except for the additional C15O scan, the procedure was the same as that described previously (Lebrun-Grandié et al. 1983). An ECAT-II (Ortec) single-slice PET device with a spatial resolution of
### Table 1.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Sex</th>
<th>Time after onset of symptoms</th>
<th>Clinical manifestations</th>
<th>CT Scan topography</th>
<th>Morphologically normal tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Gray matter</td>
</tr>
<tr>
<td>1</td>
<td>Control subject</td>
<td>M 57</td>
<td>12</td>
<td>Transient aphasia; transient right hemiparesis and aphasia</td>
<td>Diffuse cortical atrophy</td>
</tr>
<tr>
<td>2</td>
<td>Control subject</td>
<td>M 58</td>
<td>1 day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>RIA</td>
<td>M 76</td>
<td>12 days</td>
<td></td>
<td></td>
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<tr>
<td>4</td>
<td>RIA</td>
<td>M 71</td>
<td>5 months</td>
<td>Left transient hemiparesis; transient aphasia</td>
<td></td>
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<tr>
<td>5</td>
<td>Ischemic stroke</td>
<td>M 68</td>
<td>17 days</td>
<td>Left hemiplegia</td>
<td></td>
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<tr>
<td>6</td>
<td>Ischemic stroke</td>
<td>F 52</td>
<td>10 days</td>
<td>Right hemiparesis</td>
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<tr>
<td>7</td>
<td>Ischemic stroke</td>
<td>F 77</td>
<td>12 days</td>
<td>Right lateral homonymous hemianopsia; right hemiplegia</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Ischemic stroke</td>
<td>M 69</td>
<td>45 days</td>
<td>Aphasis</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Astrocytoma grade 4</td>
<td>M 67</td>
<td>17 days</td>
<td>Dyscalculia; left neglect; mild left pyramidal syndrome</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Metastasis</td>
<td>M 53</td>
<td>3 months</td>
<td>Headache</td>
<td></td>
</tr>
</tbody>
</table>

**Clinical manifestations:**
- Transient aphasia; transient right hemiparesis and aphasia
- Left transient hemiparesis; transient aphasia
- Left hemiplegia
- Right hemiparesis
- Right lateral homonymous hemianopsia; right hemiplegia
- Aphasis
- Dyscalculia; left neglect; mild left pyramidal syndrome
- Headache

**CT Scan topography:**
- Diffuse cortical atrophy
- Normal
- Right frontotemporal parietal hypodensity
- Left capsulolenticular hypodensity
- Left occipital and left capsulolenticular hypodensities
- Right temporal hypodensity
- Right parietal enhancing area
- Right frontal small enhancing ring with central hypodensity; large mass effect

**Gray matter:**
- CBF
- OEF
- OEFc
- Δ%
- CMRO₂c

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBF</td>
<td>52</td>
<td>0.52</td>
</tr>
<tr>
<td>OEF</td>
<td>0.47</td>
<td>0.07</td>
</tr>
<tr>
<td>OEFc</td>
<td>0.47</td>
<td>0.07</td>
</tr>
<tr>
<td>Δ%</td>
<td>11</td>
<td>3.8</td>
</tr>
<tr>
<td>CMRO₂c</td>
<td>11.0</td>
<td>3.5</td>
</tr>
</tbody>
</table>

* Reversible ischemic attack as defined by Loeb (1978)

16 mm on the lateral plane and 19 mm on the axial plane (slice thickness) was used.

In the C15O₂ and ¹⁵O₂ scans, about 1 million true-coincidence counts were collected after equilibrium had been reached, while in the C15O scan, about 400,000 true-coincidence counts were collected. The duration of the entire procedure was about 90 min.

During each emission scan, arterial blood samples were obtained (radial artery catheter), and the arterial content of H₂¹⁵O, Hb¹⁵O₂, and Hb-C¹⁵O was measured in both whole blood and plasma using a well-counter cross calibrated with the ECAT system.

#### Image processing

The ¹⁵O₂ images were corrected, pixel by pixel, for the ¹⁵O activity present in blood spaces using the following equation (derived by Lammertsma and Jones 1983):

$$A_{1c} = \frac{A_2 \cdot |CO|}{A_2 \cdot |CO| - A_3 \cdot |CO_2|} - \frac{A_3}{|CO|} (|Hb| + |H_2O|)$$

where $A_1 = $ brain activity during the ¹⁵O₂ scan; $A_{1c} = $ brain activity during the ¹⁵O₂ scan corrected for intravascular activity; $A_2 = $ brain activity during the C¹⁵O₂ scan; $A_3 = $ brain activity during the C¹⁵O scan; $|CO| = $ arterial concentration of C¹⁵O; $|CO_2| = $ arterial concentration of H₂¹⁵O during the C¹⁵O₂ scan; $|Hb| = $ arterial concentration of Hb-¹⁵O₂ during the ¹⁵O₂ scan; $|H_2O| = $ arterial concentration of H₂¹⁵O during the ¹⁵O₂ scan.

For purposes of comparison, both the uncorrected and corrected OEF images were obtained by dividing, pixel by pixel, the uncorrected and corrected ¹⁵O₂ images, respectively, by the C¹⁵O₂ image (Jones et al. 1976). The CMRO₂ images were obtained by the usual procedure, i.e., CMRO₂ = CBF x OEF x Cₐ, where Cₐ is the total arterial oxygen content.