Inhalation Imaging with Oxygen-15 Labeled Carbon Dioxide for Detection and Quantitation of Left-to-Right Shunts

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SUMMARY  Quantitation of left-right shunts was determined noninvasively from the pulmonary clearance pattern of inhaled \(^{15}\)oxygen-labeled carbon dioxide \((C^{15}O_2)\). After a single breath inhalation of \(C^{15}O_2\), counts over the lungs were obtained from sequential 0.5 sec positron camera images. In 21 patients without left-to-right shunts, counts declined exponentially due to the washout of \(C^{15}O_2\) by the pulmonary blood flow. In 22 patients with left-to-right shunts, this monoeponential pulmonary clearance pattern was interrupted by an abnormal upward deviation, indicating tracer recirculation through the shunt to the lungs. Following surgical shunt closure in 10 patients, pulmonary \(C^{15}O_2\) clearance patterns became normal in nine and showed a small residual left-to-right shunt in one. Shunt size was derived from the ratio of the height of the recirculation curve to the height of the initial inhalation peak. These values significantly correlated with shunt size as determined by oximetry \((r = 0.83)\).

NONINVASIVE RADIONUCLIDE TECHNIQUES have successfully been employed for detection and quantitation of left-to-right shunts. Blood flow through a shunt is assessed by the intravenous administration of a radionuclide and externally monitoring its circulation through the lungs with a scintillation camera or probe. The most widely reported radionuclide method employs the intravenous injection of a \(^{99}\)technetium-labeled radiopharmaceutical. After an initial passage of the radiotracer through the pulmonary circulation, any early reappearance of tracer activity in the lungs represents flow through the shunt. The magnitude of this abnormal recirculation curve is proportional to the magnitude of the shunt. Although this method of shunt quantitation correlates well with shunt quantitation as determined by the Fick method at cardiac catheterization, it may be limited by dispersion of the bolus of radioactivity during passage through the right-sided chambers and pulmonary vascular bed. An alternative to the intravenous route is to administer the tracer bolus closer to the origin of the shunt, as with inhalation of a radioactive gas which rapidly diffuses into the pulmonary venous blood. An advantage of this technique is that the lungs become both the site of administration and the site of sampling. In this report, we describe our clinical experience with a method of left-to-right shunt detection and quantitation which employs a single breath inhalation of \(^{15}\)oxygen-labeled carbon dioxide \((C^{15}O_2)\) and the monitoring of its washout from the lungs by sequential imaging with a multicrystal positron camera.

Materials and Methods

Patients

Forty-seven patients ranging in age from 15 to 79 years underwent \(C^{15}O_2\) inhalation imaging after giving informed consent. Only patients undergoing cardiac catheterization

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\[\text{Supported in part by NIH Grant HL 15860-03, USPHS Grant HL 17665-02, and AHA Grant-in-Aid 76-412. Dr. Beller is an Established Investigator of the American Heart Association.}
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\[\text{Received August 6, 1976; revision accepted May 9, 1977.}
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were included. Twenty-two patients had intracardiac or great vessel left-to-right shunts and are listed in table 1. Of these, 17 had imaging studies performed within 24 hours of cardiac catheterization. Nineteen patients had left-to-right shunts with no right-to-left shunt and included 12 with atrial septal defects, four with ventricular septal defects, one with partial anomalous pulmonary venous drainage, one with a partial atrioventricular canal defect and one with a coronary arteriovenous fistula. Three patients had bidirectional shunting, and included one with a tetralogy of Fallot and a surgical Blalock-Taussig shunt, one with a single ventricle and pulmonic stenosis, and one with a complete atrioventricular canal defect and pulmonic stenosis. Four patients had congestive heart failure, but none had radiographically evident pulmonary edema at the time of the imaging study. Four patients had coexisting valvular regurgitation. Ten patients underwent surgical shunt closure and all had repeat \(C^{15}O_2\) inhalation imaging studies in the postoperative period.

Twenty-one patients without a left-to-right shunt were studied and comprised the control group. Of these, 17 had angina pectoris, two had mild pulmonic stenosis, one had coarctation of the aorta and large intercostal collaterals, and one had Ebstein’s anomaly. The latter patient demonstrated a right-to-left shunt with no left-to-right shunt at cardiac catheterization. Four additional patients without a left-to-right shunt were studied at a time of severe hemodynamic deterioration due to primary pulmonary hypertension in two and advanced left ventricular failure in two.

Scintigraphic Techniques

In these studies, scintigraphy was performed using a multicrystal positron camera. This system uses multiple coincidence detection of positron annihilation radiation for collimation. The camera has two identical detector heads positioned for detection of the gamma rays emitted in opposite directions upon annihilation of a positron. The coincident data is stored in a magnetic-core memory and used for local display, or transferred under program control for processing to a computer system (MODCOMP 11). Processed images are then viewed on an oscilloscope with a 128 \(\times\) 128 raster with 64 intensity levels.

The short-lived positron-emitting isotope, \(^{15}\)oxygen \((T 1/2\)
was incorporated as an oxide of carbon by breathing it with activated charcoal at 600°C. Any carbon monoxide produced was converted to carbon dioxide by passing the gas over cupric oxide heated to 500°C. The result was an air mixture with approximately 3% carbon dioxide having a trace amount of sterile C¹⁴O₂ which was piped from the cyclotron to the positron camera area for imaging studies.

All patients were studied in the supine position with the two detector heads placed above and below for anteroposterior imaging. Transmission images of the lungs with a plane source of ⁶⁷gallium-ethylene diamine tetraacetic acid were used to accurately position the patient within the 27 × 30 cm field of the camera. Approximately 1 mCi of C¹⁴O₂ in 50 cc of air was inhaled at the onset of a single tidal volume followed by ten seconds of breath holding without a Valsalva maneuver.

Twenty consecutive 0.5 second images were collected beginning one second prior to and for nine seconds after inhalation of the bolus of C¹⁴O₂. Images in the sequence were visually evaluated as they were serially displayed on the computer oscilloscope. The 0.5 second image obtained immediately after inhalation contained approximately 10,000 counts. Oxygen-15 activity in the upper one-half of both lung fields and in the heart area was measured in each image by delineation of "regions of interest" over these zones and computer processing. Regional ¹⁵O activity in the right and left upper lobes and the right lower lobe were plotted against time after inhalation. Since normal pulmonary clearance of C¹⁴O₂ follows a single exponential decline, time-activity curves were plotted on semilog paper.⁷,¹⁵,¹⁷ In all patients a straight line was manually drawn through the points from peak inhalation to the appearance of maximum activity in the heart region. Since in the absence of a left-to-right shunt the washout pattern remains linear,¹⁵,¹⁷ a straight line can be fitted to the entire downslope of activity. In the presence of a left-to-right shunt, the initial lung clearance is interrupted by an abnormal upward deviation representing early recirculation of tracer through the shunt to the lungs.¹²,¹³,¹⁷ In these shunt patients, a curve was manually fitted to the points comprising the first recirculation by one of the investigators who had no knowledge of the results of catheterization.

Quantitation of Shunt Size

The magnitude of a left-to-right shunt was expressed by the shunt fraction, that is the fraction of total pulmonary blood flow representing shunt flow. The shunt fraction is related to the pulmonary-to-systemic flow ratio (Qp/Qs) in the following manner: 

\[ \text{Shunt fraction} = \frac{\text{Qp}}{\text{Qs}} \]

The shunt fraction value is more sensitive than Qp/Qs since in the presence of a bidirectional shunt, the Qp/Qs ratio only reflects the net shunt flow and not the magnitude of the left-to-right component. The shunt fraction was quantitated from the semilog plots of pulmonary C¹⁴O₂ clearance employing the formula derived by Tamer et al.¹⁶ As shown in figure 1, this method involves extrapolation of the initial downslope of activity below the recirculation curve and using a modified height ratio calculation to determine shunt fraction. As derived by Tamer et al.,¹⁶ shunt fraction equals the ratio of the maximum height of the first recirculation curve above the extrapolated linear downslope (H₂) to the height of initial peak activity after inhalation (H₁), multiplied by the base of the natural logarithm, e, which equals

### Table 1. Cardiac Diagnoses and Shunt Fractions in Patients with Left-to-Right Shunts

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age/sex</th>
<th>Shunt</th>
<th>Associated lesion</th>
<th>Shunt fraction C¹⁴O₂ Oximetry</th>
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<tbody>
<tr>
<td>1</td>
<td>18M</td>
<td>ASD</td>
<td>none</td>
<td>.30</td>
</tr>
<tr>
<td>2</td>
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<td>ASD</td>
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<td>3</td>
<td>20F</td>
<td>ASD</td>
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<td>.67</td>
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<tr>
<td>6</td>
<td>45F</td>
<td>ASD</td>
<td>none</td>
<td>.66</td>
</tr>
<tr>
<td>7</td>
<td>46F</td>
<td>ASD</td>
<td>none</td>
<td>.94</td>
</tr>
<tr>
<td>8</td>
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<td>ASD</td>
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<td>.89</td>
</tr>
<tr>
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<td>63F</td>
<td>ASD</td>
<td>CHF</td>
<td>.58</td>
</tr>
<tr>
<td>11</td>
<td>63F</td>
<td>ASD</td>
<td>none</td>
<td>.68</td>
</tr>
<tr>
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<td>71M</td>
<td>ASD</td>
<td>CHF, TR</td>
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</tr>
<tr>
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<td>15M</td>
<td>VSD</td>
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<td>.16</td>
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<td>26F</td>
<td>VSD</td>
<td>AR</td>
<td>.35</td>
</tr>
<tr>
<td>15</td>
<td>26M</td>
<td>VSD</td>
<td>CHF, AR</td>
<td>.38</td>
</tr>
<tr>
<td>16</td>
<td>74F</td>
<td>VSD</td>
<td>CHF</td>
<td>.73</td>
</tr>
<tr>
<td>17</td>
<td>27F</td>
<td>PAPVR</td>
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<td>.24</td>
</tr>
<tr>
<td>18</td>
<td>34M</td>
<td>PAVCD</td>
<td>PHT, MR</td>
<td>.61</td>
</tr>
<tr>
<td>19</td>
<td>18F</td>
<td>CAVF</td>
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<td>.21</td>
</tr>
<tr>
<td>20</td>
<td>16M</td>
<td>Blalock</td>
<td>R→L shunt, TF</td>
<td>.53*</td>
</tr>
<tr>
<td>21</td>
<td>17F</td>
<td>SV</td>
<td>R→L shunt, PS</td>
<td>.51</td>
</tr>
<tr>
<td>22</td>
<td>18F</td>
<td>CAVCD</td>
<td>R→L shunt, PS</td>
<td>.65</td>
</tr>
</tbody>
</table>

*Refers to left lung only.

Abbreviations: AH = aortic regurgitation; ASD = atrial septal defect; CAVCD = complete atrioventricular canal defect; CAVF = coronary arteriovenous fistula; CHF = congestive heart failure; MR = mitral regurgitation; NA = not available; PAPVR = partial anomalous pulmonary venous return; PAVCD = partial atrioventricular canal defect; PHT = pulmonary hypertension; PS = pulmonic stenosis; R→L = right-to-left; SV = single ventricle; TF = tetralogy of Fallot; TR = tricuspid regurgitation; VSD = ventricular septal defect.

**Figure 1.** The formula for calculation of left-to-right shunt fraction from the pulmonary clearance pattern of inhaled C¹⁴O₂ is shown. Shunt fraction is proportional to the ratio of the height of the recirculation peak to the height of initial peak activity.
2.72. The extrapolation of the initial clearance predicts the amount of tracer expected to be present in the lung at any time if the rate of washout continued unaltered by shunt flow. As illustrated in figure 1, this value must be subtracted from counts actually measured during recirculation in order to determine the amount of tracer present in the lung due solely to left-to-right shunt flow (H₂). Subtraction of this extrapolated value is an essential step of this and similarly described radionuclide methods for quantitating the magnitude of left-to-right shunts.

Cardiac Catheterization Studies

In 21 of the 22 patients in the shunt group, shunt fraction was also determined by oximetry at cardiac catheterization employing the Fick principle. The mixed venous sample was calculated as 3/4 superior vena cava oxygen content + 1/4 inferior vena cava oxygen content. One patient had a shunt demonstrated by angiography alone. Linear regression analysis was performed on the values for shunt fraction obtained by the two methods: C¹⁵O₂ inhalation imaging and oximetry.

Figure 2. Left) Serial 0.5 second positron camera images of C¹⁵O₂ activity in a normal patient taken 2, 4, and 6 sec after peak inhalation (0 sec). Various regions of interest delineated by dotted squares are placed over the lung fields and heart area. These images show normal washout of tracer from the lungs and accumulation of activity in the heart region. Lung activity is almost entirely cleared by 6 seconds. Right) Serial 0.5 second positron camera images of C¹⁵O₂ activity obtained 2 and 4 seconds after peak inhalation (0 sec) in patient #5 with an atrial septal defect. In this patient, normal pulmonary washout of tracer is observed at 2 seconds, but 4 seconds after inhalation there is early reappearance of activity in the lungs reflecting left-to-right shunt flow.
Rates of Initial C\textsubscript{18}O\textsubscript{2} Clearance

After inhalation, C\textsubscript{18}O\textsubscript{2} rapidly diffuses into the pulmonary blood and its rate of clearance is proportional to pulmonary blood flow.\textsuperscript{19} In order to investigate whether any change in pulmonary blood flow occurred after surgical shunt correction, linear regression analysis was performed on the initial portion of the downslope for both pre and postoperative pulmonary activity curves. The resultant values (log counts/sec) for the two studies were compared.

Statistical Analysis

The linearity of the semilog plot of the lung C\textsubscript{18}O\textsubscript{2} clearance curve was determined by a least squares fit to the logarithm of the count values versus time. From this analysis, the correlation coefficient, slope and variance for the best fit line was derived. The significance of a change in the rate of initial C\textsubscript{18}O\textsubscript{2} clearance was determined by comparison of the pre and postoperative slopes by t-test, employing pooled variance estimates.\textsuperscript{20} Values of shunt fraction determined by C\textsubscript{18}O\textsubscript{2} inhalation and oximetry were compared in the same patient by least squares analysis.

Results

The age, sex, clinical diagnoses and shunt fractions determined by C\textsubscript{18}O\textsubscript{2} inhalation and oximetry in 22 patients studied with left-to-right shunts are summarized in table 1. In all, pulmonary clearance patterns demonstrated a rapid initial C\textsubscript{18}O\textsubscript{2} washout which was interrupted by a well defined abnormal upward deviation from linearity, representing early tracer recirculation through the shunt to the lungs. In the 21 hemodynamically stable nonshunt patients, the pulmonary washout of C\textsubscript{18}O\textsubscript{2} showed no deviation from linearity during the 10 sec imaging period. Correlation coefficients for the lines as fitted to the data points in each patient ranged from 0.960 to 0.995. Figures 2 and 3 show sequential images and C\textsubscript{18}O\textsubscript{2} clearance patterns in representative patients from the normal and left-to-right groups. In patients with left-to-right shunts, the presence of the shunt could be qualitatively ascertained by visual inspection of the serial 0.5 second images as illustrated in figure 3. Early reappearance of C\textsubscript{18}O\textsubscript{2} activity in the lungs was observed within the first 5 seconds after inhalation of the C\textsubscript{18}O\textsubscript{2} bolus. There were no false positive or false negative results in this patient population.

As shown in table 1, the range of shunt fractions measured by C\textsubscript{18}O\textsubscript{2} inhalation scanning in these patients was 0.16 to 0.94. One patient (#19) with a small left-to-right shunt due to a coronary arteriovenous fistula was studied. Although this shunt was clearly demonstrated by coronary angiography, the oxygen step-up measured at catheterization was not large enough to be considered significant according to established criteria.\textsuperscript{21} Figure 4 shows the semilog plot of pulmonary C\textsubscript{18}O\textsubscript{2} clearance in this patient. Although the magnitude of the early recirculation curve is small, there is a definite break from linearity indicative of a small left-to-right shunt.

The left-to-right component of a bidirectional shunt was determined in three patients and correlated well with values

![Figure 3. Left] Semilog plot of regional C\textsubscript{18}O\textsubscript{2} counts (vertical axis) versus time after peak inhalation (horizontal axis) in a normal patient. Lung clearance of C\textsubscript{18}O\textsubscript{2} (solid circles) is linear over the time period shown. Regional activity in the heart region (open circles) is noted by 3 seconds. Right) Semilog plot of regional C\textsubscript{18}O\textsubscript{2} counts (vertical axis) versus time after peak inhalation (horizontal axis) in the patient with an atrial septal defect whose serial positron images are shown in figure 2 right. The initial washout of C\textsubscript{18}O\textsubscript{2} activity from the right upper lung is linear, but is interrupted by an abnormal upward deviation indicating early recirculation of tracer through the shunt to the lungs. Regional counts in the heart region are depicted by open circles.
Lung clearance are noted only in the left lung, as might be expected with patency of the Blalock-Taussig anastomosis. Presumably because of markedly diminished blood flow, clearance from the poorly perfused right lung was reduced.

Repeat inhalation imaging studies were performed in 10 patients following surgical shunt closure. In nine patients, the pulmonary clearance pattern of C15O2 became normal. Figures 7 and 8 show pre and postoperative C15O2 clearance measured by oximetry (table 1). Figure 5 shows the abnormal pulmonary C15O2 washout in one of these patients (#21) who had a single ventricle and pulmonic stenosis. Another one of these patients (#20) had a surgically created left-to-right shunt to the left lung for a tetralogy of Fallot. As shown in figure 6, C14O2 washout and subsequent early recirculation are noted only in the left lung, as might be expected with patency of the Blalock-Taussig anastomosis. Washout of tracer from the left lung is observed in the image obtained 3 seconds after inhalation. Early reappearance of activity in the left lung is observed in the image obtained at 5 seconds and reflects left-to-right shunt flow through the patent anastomosis. In contrast, there is little washout of C14O2 from the poorly perfused right lung during this period of time.
patterns in two of these patients. The postoperative study in the one remaining patient in this group (6) showed a small residual left-to-right shunt with a shunt fraction of 0.23. Values for the rate of initial C1502 lung clearance (log10 counts/sec) were compared before and after shunt closure in all 10 patients and are presented in Table 2. In five of these patients, there was a significant reduction in the rate of tracer washout postoperatively consistent with reduction in pulmonary blood flow secondary to shunt closure. This is reflected by a more gentle slope of initial C1502 clearance, as

Figure 7. C1502 clearance patterns in patient #11 with a large atrial septal defect before (left panel) and after (right panel) surgical shunt closure. In the preoperative study, a large left-to-right shunt is evident. Postoperatively, the C1502 pulmonary washout pattern is normal with no deviation from linearity. The slope of the initial lung clearance (0 to 2.5 seconds) has become less steep postoperatively, indicating a slower washout of tracer attributed to a reduction in the abnormally increased pulmonary blood flow resulting from the shunt.

Figure 8. Pre and postoperative C1502 inhalation studies in patient #16 with a ventricular septal defect and congestive heart failure after a myocardial infarction. The preoperative pulmonary clearance of C1502 demonstrates an early recirculation peak indicative of left-to-right shunting. The postoperative clearance pattern is normal, suggesting successful closure of the defect. The postoperative study shows a more rapid washout rate, suggesting an improvement in hemodynamics with resolution of heart failure.
illustrated in figure 8. Preoperative shunt fractions in these patients were 0.75 or greater. In four patients with relatively smaller shunt flows (shunt fractions 0.43 to 0.61) and including the patient with the residual left-to-right shunt, there was no significant change in the rate of C1502 clearance after shunt closure. The remaining patient in this group showed a more rapid rate of C1502 lung washout after surgery suggesting an increase in pulmonary blood flow. As shown in figure 8, this was reflected as a steeper slope of initial tracer clearance. This patient had a ventricular septal defect complicating an inferior myocardial infarction. Congestive heart failure and low cardiac output were evident preoperatively. Shunt closure and aneurysmectomy in the patient may have resulted in an increased cardiac output which would account for the increased rate of pulmonary C1502 clearance measured in the postoperative imaging study. The rate of pulmonary clearance of C1502 was markedly reduced in two patients with primary pulmonary hypertension and in two patients with severe left ventricular failure and radiographic evidence of pulmonary edema. None had coexisting left-to-right shunts. Figure 9 shows the C1502 clearance pattern obtained in one of these patients.

Shunt fraction values determined by C1502 inhalation imaging were compared with shunt fraction values determined by oximetry in 21 of the shunt patients. As shown in figure 10, the correlation between the two methods was good ($r = 0.83$).

The patient radiation dose with this technique is minimal. After inhalation of 1 mCi of $^{15}$O activity, the absorbed dose to the lungs is 3 mR and the total body dose is 1.5 mR.

**Discussion**

Indicator-dilution methods have been extensively used for detection and quantitation of left-to-right shunts, but usually require intravascular catheterization for dye injection and sampling.$^{21, 22}$ The use of intravenously administered radionuclides as indicators has permitted the noninvasive quantitation of left-to-right shunts.$^*$ Activity of the tracer is monitored externally by a single scintillation probe or a scintillation camera as it recirculates through the lungs.$^*$ In the presence of a left-to-right shunt, an initial transit of the radiopharmaceutical is followed within several seconds by a separate pulmonary transit due to flow across the shunt. This method has been successfully employed in patients and a good correlation of shunt size compared with that determined by oximetry has been shown.$^{10}$

Essential to these indicator-dilution methods is delivery of the indicator as a bolus. After intravenous injection, fragmentation of the bolus may occur during the passage through the venous circulation and right heart. This may represent a particular problem in the setting of significant valvular regurgitation or congestive heart failure, in which case an uninterpretable or false positive transit pattern may result.$^2, ^*$ Injection of the tracer into a central vein partially alleviates this problem.$^8$ Bolus dispersion can be even further minimized by inhaling the radioindicator, thereby avoiding

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**Table 2. Comparison of Rates of $^{15}$O2 Washout Before and After Surgical Correction of a Left-to-Right Shunt**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Washout rate (log counts/second + m)</th>
<th>Preop</th>
<th>Postop</th>
<th>Change</th>
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<tbody>
<tr>
<td>1</td>
<td>-0.088 ± 0.005</td>
<td>-0.090 ± 0.012</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>2</td>
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<td>-0.093 ± 0.005</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>-0.118 ± 0.014</td>
<td>-0.064 ± 0.004</td>
<td>Decrease**</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>-0.104 ± 0.10</td>
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<td></td>
</tr>
<tr>
<td>7</td>
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<td>-0.063 ± 0.007</td>
<td>Decrease***</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>-0.235 ± 0.021</td>
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<td>Decrease*</td>
<td></td>
</tr>
<tr>
<td>11</td>
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<td>-0.071 ± 0.012</td>
<td>Decrease***</td>
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</tr>
<tr>
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<td>NS</td>
<td></td>
</tr>
<tr>
<td>16</td>
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</tr>
<tr>
<td>18</td>
<td>-0.202 ± 0.013</td>
<td>-0.162 ± 0.017</td>
<td>Decrease**</td>
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</table>

*p < 0.05.
**p < 0.01.
***p < 0.005.
passage through the right-sided chambers. Oxygen-15 labeled carbon dioxide is uniquely suited for this purpose, because it rapidly diffuses into the pulmonary venous blood. The presence of carbonic anhydrase in the lung results in rapid equilibration of oxygen-15 from the inhaled C15O2 with the oxygen of water and bicarbonate via carbonic acid.17 Because the amount of water in the pulmonary blood flow far exceeds that of dissolved carbon dioxide or bicarbonate, most of the oxygen labels water with only a small amount remaining in dissolved carbon dioxide or bicarbonate. Thus, inhaled C15O2 rapidly enters the pulmonary venous blood as H215O, resulting in the bolus delivery necessary for indicator-dilution analysis.

Following C15O2 inhalation, both initial lung clearance and subsequent recirculation to the lung can be externally monitored as with intravenous methods.18 The clearance rates for C15O2 are comparable to those observed following a discrete intravascular injection of an intravenous tracer.4 Recently, Watson and co-workers, using a single scintillation probe directed over the lung, described a method for shunt quantitation employing the pulmonary clearance pattern of inhaled C15O2.12, 18 The initial portion of the clearance pattern is monoexponential. By plotting the pulmonary clearance of C15O2 on a semilog scale, abnormal early recirculation of tracer represents flow through the left-to-right shunt. The height of the recirculation peak resulting from left-to-right shunt flow can be determined by inspection of the semilog plot. Shunt fraction can then be calculated from the ratio of this peak to the counts measured immediately after inhalation of the C15O2 bolus.18

The use of a sequential imaging technique after C15O2 inhalation to analyze left-to-right shunts has not been previously reported. Presently, a conventional gamma scintillation camera cannot be used for imaging with positron-emitting isotopes since the energy of the 511 keV gamma emissions is too high for adequate collimation. In this study, the use of inhalation imaging with C15O2 and a positron camera for visual detection and subsequent quantitation of left-to-right shunts has been demonstrated. A positron camera, through coincidence techniques, can achieve the collimation necessary for C15O2 imaging, and pulmonary time-activity data employed to measure shunt size can be obtained from computer-derived regions of interest defined within the sequential images.

In this study, C15O2 inhalation imaging was performed in 47 patients. In all 22 patients with a left-to-right shunt, the C15O2 pulmonary clearance pattern showed an abnormal early reappearance of activity in the lung region due to shunt flow. There were no false negative studies. In all control patients, pulmonary clearance of C15O2 was linear throughout the 10 second imaging period and no false positive studies were observed. The control group included a patient with a coarctation of the aorta without a left-to-right shunt who had a normal C15O2 lung washout despite an extensive intercostal collateral circulation, which might have resulted in a false positive test. This method appears to be quite sensitive in that shunts as small as 1.2:1 could be measured. When the shunt fraction determined by C15O2 inhalation imaging was compared to shunt fraction as determined by oximetry in the shunt group, the correlation coefficient was 0.83. This compares favorably with other noninvasive radioisotope techniques for shunt quantitation, in which correlation coefficients have ranged from 0.72 to 0.88.9 The correlation between noninvasive and invasive techniques appears good considering the potential errors inherent in oximetry determinations.21 Another possible explanation for discrepancy in values between the two methods is that imaging and catheterization studies were not performed at the same time, and shunt flows may have differed at the time of each procedure.

Left-to-right shunts were successfully quantitated in four patients with valvular regurgitation, in four patients with mild heart failure, and in three patients with biventricular hypertension. In another patient with a pure right-to-left shunt due to Ebstein’s anomaly, a left-to-right shunt was excluded. Quantitation of a left-to-right shunt in the presence of bidirectional shunting is not possible using intravenous indicator methods, because the tracer is injected on the right side of the circulation and flow through the right-to-left shunt fragments the bolus before the tracer reaches the left heart.7 This represents one of the distinct advantages of administering the radioactive indicator by inhalation rather than by the intravenous route. One patient, age 15, had a palliative Blalock-Taussig anastomosis at age 4 for severe tetralogy of Fallot. Pulmonary clearance of C15O2 from the underperfused right lung was found to be abnormally slow, but tracer washout from the left lung was rapid and was associated with an early recirculation curve corresponding to a left-to-right shunt fraction of 0.55. This clearance pattern for the left lung confirmed the patency and substantial flow through the surgical anastomosis. In two other patients with bidirectional shunts, the inhalation study was not consistent with the precatheterization clinical diagnosis of tetralogy of Fallot. In these studies, the rapid washout of tracer from both lungs suggested a normal or an increased rather than the decreased pulmonary blood flow usually observed in tetralogy of Fallot. Indeed, at the time of catheterization, an alternative explanation for a left-to-right shunt was sought and found in both patients. One patient had a single ventricle with pulmonic stenosis and the other had a common atroventricular canal defect with pulmonic stenosis. These congenital lesions have different surgical management implications than isolated tetralogy of Fallot.

In the present study, pulmonary clearance of C15O2 was found to be abnormally slow in the presence of reduced pulmonary perfusion in a patient with tetralogy of Fallot, in two patients with primary pulmonary hypertension with no left-to-right shunt and in two patients with severe heart failure, low cardiac output and no shunt. The rate of pulmonary C15O2 clearance also appeared reduced in another patient who developed a ventricular septal defect and heart failure after a posterior myocardial infarction. A second imaging study after surgical correction of the defect in this patient showed a faster clearance of tracer coincident with an improved hemodynamic status. Patients with primary pulmonary hypertension demonstrated an abnormally slow C15O2 washout, presumably related to a chronic reduction in pulmonary blood flow. Interestingly, a normal rate of C15O2 washout was observed in the patient with severe pulmonary hypertension and a persistent left-to-right shunt. These findings confirm prior observations that the rate of C15O2 washout is related to pulmonary blood flow.19
Although not observed in the present study, another potential cause for slow pulmonary clearance of C\textsuperscript{15}O\textsubscript{2} might be the presence of pulmonary edema, in which the increased lung water competes with water in the pulmonary vascular bed for oxygen-15.\textsuperscript{27} Only the portion of the H\textsubscript{2}\textsuperscript{15}O in the latter compartment is washed out rapidly. In these patients, the slow washout could result in dispersion of the bolus of H\textsubscript{2}\textsuperscript{15}O entering the left heart and left-to-right quantitation might become less reliable.

A single scintillation probe can successfully be employed to obtain C\textsubscript{15}O\textsubscript{2} time-activity curves for shunt quantitation.\textsuperscript{12, 13, 14} In the present study, a positron camera was employed to obtain dynamic images of the lung fields in addition to quantitating regional \textsuperscript{15}O activity. These dynamic images were collected over very short time intervals (0.5 sec) and because of low counting statistics, image quality does not compare to that observed with conventional lung scanning. On the other hand, positron imaging has the advantage of spatial resolution and will ultimately provide more information than single probe studies when technology is sufficiently developed to retain statistical validity to images. At present, the data are sufficient to extract dynamic function curves of pulmonary C\textsubscript{15}O\textsubscript{2} clearance. In addition, visualization of serial positron images assures accurate placement of “regions of interest” over the portion of lung fields from which quantitative information is obtained. For example, in one patient with dextroversion associated with an atrial septal defect, only the left lung was visualized. At surgery, the right lung was found to be severely hypoplastic. Hence, during the imaging procedure, the C\textsubscript{15}O\textsubscript{2} washout curve was derived from the normal left lung. Imaging of C\textsubscript{15}O\textsubscript{2} distribution in the lungs may also be of value in patients with chronic pulmonary disease. Abnormal regional ventilation would result in inhomogeneous delivery of C\textsubscript{15}O\textsubscript{2} and pulmonary activity curves might be difficult to generate from certain regions of the lungs.\textsuperscript{29}

In summary, this study demonstrates that sequential positron imaging after a single breath inhalation of oxygen-15 labeled carbon dioxide can be successfully employed for detection and quantitation of left-to-right shunts. Although only adult or adolescent patients with left-to-right shunts were studied, the C\textsubscript{15}O\textsubscript{2} inhalation method for shunt detection and quantitation can successfully be employed in patients in the pediatric age group.\textsuperscript{18} This technique is totally noninvasive and highly specific and sensitive. The values obtained for shunt size with this method correlate well with values obtained by oximetry at catheterization. In contrast to radionuclide methods employing intravenous tracer administration, the inhalation route of tracer delivery permits the quantitation of the left-to-right component of a bidirectional shunt. By this technique, shunt size can be measured in patients with heart failure and valvular regurgitation. Finally, the radiation dose to the patient is minimal because of the ultra-short half-life of oxygen-15.

Acknowledgment

The authors are grateful to Dr. Denny D. Watson for his technical advice and to Dr. John B. Newell, who performed the statistical analyses.

References

Inhalation imaging with oxygen-15 labeled carbon dioxide for detection and quantitation of left-to-right shunts.
C A Boucher, B Ahluwalia, P C Block, G L Brownell and G A Beller

Circulation. 1977;56:632-640
doi: 10.1161/01.CIR.56.4.632

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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