Resolution Rates of Pulmonary Embolism Assessed by Serial Positron Imaging with Inhaled 0-15-Labeled Carbon Dioxide

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Embolic obstruction of pulmonary blood flow results in delayed regional clearance of inhaled C\textsuperscript{15}O\textsubscript{2}. Focally retained C\textsuperscript{15}O\textsubscript{2} appears as zones of increased O-15 activity on serial positron scintigrams, which show the locations of occluded pulmonary segments. Inhalation of C\textsuperscript{15}O\textsubscript{2}, with serial imaging by a multicrystal positron camera, was used to locate and assess the magnitude of occluded pulmonary segments in eight patients with arteriographically documented pulmonary emboli. The imaging with C\textsuperscript{15}O\textsubscript{2} inhalation was repeated after 1 wk of i.v. heparin therapy to evaluate the ability of this technique to determine resolution rates of pulmonary emboli during anticoagulant therapy. In all patients, zones of increased C\textsuperscript{15}O\textsubscript{2} activity corresponded with sites of emboli identified arteriographically. After 1 wk of continuous heparin therapy, zones of focally retained C\textsuperscript{15}O\textsubscript{2} were totally resolved in three patients, diminished in four, and unchanged in one. The regional pulmonary clearance rate of C\textsuperscript{15}O\textsubscript{2} was delayed over embolized pulmonary segments in all patients (mean clearance half-time = 42.2 sec ± 11.2 s.e.m.) and improved after heparin therapy (13.9 ± 3.9 sec; p < 0.05). Serial C\textsuperscript{15}O\textsubscript{2} inhalation imaging is a rapid noninvasive radionuclide technique for detection of pulmonary emboli. It can be repeated at frequent intervals to assess the resolution of emboli during anticoagulant therapy.


In 1960 West et al. (1) first described the physiologic mechanism that explains the rapid uptake of oxygen-15-labeled carbon dioxide by the lung. They demonstrated that C\textsuperscript{15}O\textsubscript{2}, administered by inhalation, diffuses rapidly across the pulmonary alveolar membrane and is hydrated by carbonic anhydrase in red cells to carbonic acid (Fig. 1). The carbonic acid dissociates to bicarbonate, yielding O-15-labeled water. Thus, single-breath inhalation of C\textsuperscript{15}O\textsubscript{2} results in very rapid labeling of pulmonary water with H\textsubscript{2}\textsuperscript{15}O. The H\textsubscript{2}\textsuperscript{15}O is normally cleared from the lungs in several seconds by pulmonary blood flow and is dispersed throughout the large body pool of unlabeled water. Because of this nearly instantaneous conversion of C\textsuperscript{15}O\textsubscript{2} to labeled water, inhaled C\textsuperscript{15}O\textsubscript{2} is readily taken up by pulmonary blood and virtually none is exhaled.

Subsequent studies in experimental animals have shown that regional clearance of inhaled C\textsuperscript{15}O\textsubscript{2} from the lung is directly proportional to regional pulmonary blood flow (2,3). West and his colleagues observed that the clearance of C\textsuperscript{15}O\textsubscript{2} in pulmonary segments distal to emboli was markedly delayed in
a patient with multiple pulmonary emboli (4). Recently, Taplin et al. (5) proposed the use of inhaled C18O2 as a means of scintigraphically detecting pulmonary emboli.

In a study of experimental pulmonary emboli in anesthetized dogs, Nichols et al. (6) demonstrated that serial positron imaging reliably detected emboli as small as 2 mm in diameter following administration of 2 mCi C18O2 by inhalation. Stasis of blood distal to emboli caused retention of O-15 activity, which permitted visualization of the location and extent of the embolized region. In a subsequent study of patients with suspected pulmonary embolism, the accuracy of C18O2 inhalation imaging was compared with conventional ventilation/perfusion imaging, with pulmonary arteriography used as the basis for comparison (7). Inhalation imaging with C18O2 was shown to be both sensitive and specific for the detection of pulmonary emboli and compared favorably with technetium-99m perfusion imaging and xenon-133 ventilation imaging.

The present study was undertaken to determine the feasibility of using single-breath C18O2 inhalation imaging to determine the rate of resolution of pulmonary emboli during anticoagulant therapy by following changes in the size of perfusion defects and alterations in regional pulmonary blood flow.

![Diagram](image)

**FIG. 1.** Schematic diagram of the pulmonary alveolus and a capillary to show mechanism whereby pulmonary blood is tagged by inhaled C18O2. The gas diffuses rapidly across the alveolar membrane and is converted by carbonic anhydrase to H2C18O3, which dissociates yielding H218O.

<p>| TABLE 1. CLINICAL FINDINGS AND RESULTS OF SERIAL C18O2 IMAGING IN PATIENTS WITH PULMONARY EMBOLI |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|</p>
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Predisposing conditions</th>
<th>Pulmonary arteriogram</th>
<th>Initial C18O2 pulmonary scan</th>
<th>Repeat C18O2 scan after 1 wk anticoagulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.G.</td>
<td>79</td>
<td>M</td>
<td>COPD</td>
<td>Multiple emboli in LUL and LLL</td>
<td>Retained O-15 activity in LUL and LLL</td>
<td>Normal O-15 clearance in LUL; diminished zone of O-15 in LLL</td>
</tr>
<tr>
<td>A.M.</td>
<td>39</td>
<td>F</td>
<td>Obesity</td>
<td>Bilateral emboli in RLL and LLL</td>
<td>Retained O-15 activity in both bases</td>
<td>Normal C18O2 scan</td>
</tr>
<tr>
<td>M.L.</td>
<td>71</td>
<td>F</td>
<td>Thrombophlebitis</td>
<td>Numerous emboli in RUL, RLL, and LLL</td>
<td>Retained O-15 activity in RUL and RLL</td>
<td>Unchanged zones of retained O-15</td>
</tr>
<tr>
<td>G.S.</td>
<td>71</td>
<td>F</td>
<td>Postoperative</td>
<td>Multiple emboli in RUL, RLL, and LLL</td>
<td>Retained O-15 in RUL and LLL</td>
<td>Normal C18O2 clearance in RUL; persistent O-15 retention in LLL</td>
</tr>
<tr>
<td>T.K.</td>
<td>71</td>
<td>M</td>
<td>Recurrent pulmonary emboli</td>
<td>Large single embolus to RLL</td>
<td>Large zone of retained O-15 in RLL</td>
<td>Slight reduction in zone of retained O-15</td>
</tr>
<tr>
<td>J.L.</td>
<td>22</td>
<td>M</td>
<td>Postoperative</td>
<td>Bilateral emboli in RLL and LLL</td>
<td>Bilateral retention of C18O2 in RLL, LLL</td>
<td>Normal C18O2 scan</td>
</tr>
<tr>
<td>N.F.</td>
<td>79</td>
<td>F</td>
<td>Obesity</td>
<td>Large embolus in LLL</td>
<td>Large zone of retained O-15 in LLL</td>
<td>Reduction in zone of retained O-15</td>
</tr>
<tr>
<td>L.C.</td>
<td>28</td>
<td>M</td>
<td>Bed rest, metastasis</td>
<td>Solitary embolus to RLL</td>
<td>Retained O-15 in RLL</td>
<td>Normal C18O2 scan</td>
</tr>
</tbody>
</table>

Abbreviations: RUL = right upper lobe, RLL = right lower lobe, LLL = left lower lobe, COPD = chronic obstructive pulmonary disease
METHODS

Positron scintigraphy with C\textsuperscript{15}O\textsubscript{2}. Oxygen-15 (T\textsubscript{1/2} = 2.1 min) was produced in a medical cyclotron by the 6 MeV-deuteron irradiation of N\textsubscript{2} + 4% O\textsubscript{2}, and was converted to C\textsuperscript{15}O\textsubscript{2} by heating over activated charcoal at 600°C (8). Serial pulmonary imaging after C\textsuperscript{15}O\textsubscript{2} inhalation was performed with a multi-crystal positron camera (9,10) in eight patients with pulmonary emboli documented by selective pulmonary arteriography. Following single-breath inhalation of 2 mCi C\textsuperscript{15}O\textsubscript{2} diluted in room air, serial positron images, each 5 sec in duration, were collected for a total of 100 sec as previously described (7).

Each patient underwent C\textsuperscript{15}O\textsubscript{2} pulmonary imaging within 48 hr of pulmonary arteriography, and C\textsuperscript{15}O\textsubscript{2} imaging was repeated after 1 wk of anticoagulant treatment with heparin. Each patient received full therapeutic doses of i.v. heparin delivered continuously by roller pump* for 7 days.

Scintigraphic analysis. Images were displayed sequentially on an oscilloscope for analysis of the pattern of clearance of C\textsuperscript{15}O\textsubscript{2} from the lungs and were photographed on Polaroid film. Oxygen-15 retained focally in the lung fields after pulmonary clearance of C\textsuperscript{15}O\textsubscript{2} was considered a positive criterion for the presence of pulmonary emboli. The location and size of the embolized segments evident on C\textsuperscript{15}O\textsubscript{2} images were compared with the location and size of emboli documented by pulmonary arteriogram.

For calculation of regional C\textsuperscript{15}O\textsubscript{2} clearance rates,
computer-derived time-activity curves were recorded from regions of interest over selected zones of the lung fields. The time-activity curves were corrected for physical decay, plotted for 5-sec intervals, and analyzed by computer with a multiexponential least-squares fit routine ([12] for the calculation of regional C\textsuperscript{14}O\textsubscript{2} clearance rates. These were measured over embolized and normally perfused pulmonary segments, calculated as per centage of activity decrease per second, and expressed as half-time values.

RESULTS

The clinical features, pulmonary arteriographic findings, and C\textsuperscript{14}O\textsubscript{2} inhalation imaging results for each patient are summarized in Table 1. Serial C\textsuperscript{14}O\textsubscript{2} images for each patient disclosed discrete zones of retained O-15 in the lung fields corresponding to the site and magnitude of the pulmonary segments occluded by emboli identified angiographically. Individual emboli ranging in size from an estimated diameter of 3 mm to massive emboli occluding the entire right or left pulmonary artery were detected on serial scans. For each patient, pulmonary clearance of C\textsuperscript{14}O\textsubscript{2} from normally perfused pulmonary segments was complete within 15 sec of C\textsuperscript{14}O\textsubscript{2} inhalation. Oxygen-15 activity retained distal to emboli remained visible on serial images for approximately 100 sec.

Shown in Fig. 2 are serial C\textsuperscript{14}O\textsubscript{2} scintigrams obtained at 5-sec intervals in a young woman with massive bilateral pulmonary emboli occluding the right pulmonary artery and inferior branch of the left pulmonary artery (Fig. 3). Within 5 sec of C\textsuperscript{14}O\textsubscript{2} inhalation, activity is distributed throughout both lung fields. By 20 sec, activity has been cleared from the left upper lobe, which is the only lobe with intact blood flow. Oxygen-15 activity is retained for more than 95 sec throughout the right lung field and the left lower lobe, which are occluded by emboli. Time-activity curves of regional O-15 clearance for this patient are shown in Fig. 4. Over the normally perfused pulmonary segment, the O-15 activity falls rapidly (T\textsubscript{1/2} = 9.8 sec) to a low background level. Clearance of O-15 activity over the occluded segment is much slower (T\textsubscript{1/2} = 95 sec) and the semilog plot is linear, indicating monoeponential clearance.

As shown in Table 1, repeat C\textsuperscript{14}O\textsubscript{2} pulmonary imaging performed after 1 wk of continuous heparin therapy demonstrated a reduction in the magnitude of the zones of retained C\textsuperscript{14}O\textsubscript{2} in four of the eight patients, complete disappearance of such areas of retained C\textsuperscript{14}O\textsubscript{2} in three young patients, and no change in one patient. Thus after 1 wk of heparin therapy, regional impairment of pulmonary blood flow resulting from emboli was either improved or became normal in all but one patient. Figure 5A shows serial positron images obtained in a 79-year-old patient (N.F.) after C\textsuperscript{14}O\textsubscript{2} inhalation. Oxygen-15 activity was retained in the left lower lobe at the site of a large embolus. Repeat C\textsuperscript{14}O\textsubscript{2} scintigrams obtained after 1 wk of heparin therapy (Fig. 5B) demonstrated significant reduction in the size of the zone of retained O-15 activity, indicating improved perfusion to the left lower lobe.

Regional C\textsuperscript{14}O\textsubscript{2} clearance rates were determined by a multi-exponential least-squares fit routine. Over normally perfused pulmonary segments, C\textsuperscript{14}O\textsubscript{2} clearance half-times ranged from 3.2 to 8.8 sec (mean 5.0 ± 0.7 s.e.m.); over embolized seg-

FIG. 3. Pulmonary arteriogram obtained during contrast injection into main pulmonary artery for patient described in Fig. 2. Right main pulmonary artery and inferior branch of left pulmonary artery were occluded by large emboli. Patient subsequently underwent successful pulmonary embolec-
FIG. 5. Top: Serial $^{14}$O positron images obtained at 5-sec intervals in elderly patient with large embolus to inferior branch of left pulmonary artery. Inhaled $^{14}$O$_2$, retained in left lower lung field, shows site and magnitude of occluded segments. Bottom: Serial positron images repeated after one week of anticoagulant therapy. Region of retained $^{14}$O$_2$ in left lung field is considerably reduced. This finding suggests improved blood flow to left lower lobe due to partial resolution of embolus.

ments they were significantly longer ($p < 0.01$), ranging from 11.7 to 100 sec (mean 42.2 ± 11.2). The clearance half-times were shorter in all patients (mean 13.9 ± 3.9 sec; $p < 0.05$) when measured again over the embolized segments after 1 wk of heparin therapy. Changes in regional $^{14}$O$_2$ clearance rates correlated with the persistence or disappearance of zones of retained $^{14}$O$_2$ on repeat scintigrams. In a patient (J.L.) with complete disappearance of focal zones of retained $^{14}$O$_2$, half-time for regional $^{14}$O$_2$ clearance over the embolized segment fell from 32 to 7 sec after 1 wk of anticoagulation. For a patient (T.K.) with only minimal reduction in the size of the zone of retained $^{14}$O$_2$ after a week of anticoagulation, the half-time for $^{14}$O$_2$ clearance fell only from 36 to 30 sec.

DISCUSSION

This study demonstrates the feasibility of using sequential $^{14}$O$_2$ inhalation imaging to monitor patients with pulmonary emboli during anticoagulant therapy. The technique is completely noninvasive and is rapidly performed, with a total imaging time of less than 2 min. Because coincidence images are collected in a single antero-posterior projection, imaging in multiple projections is unnecessary, and a study can be completed in less than 5 min. Because of the short physical half-life of $^{18}$O$_2$, radiation exposure to a 70 kg man, after inhalation of 3 mCi of $^{14}$O$_2$ is 9 mR to the lungs and 4.5 mR to the whole body.

A useful feature of $^{14}$O$_2$ imaging is that it provides a means of noninvasively assessing residual perfusion in pulmonary segments distal to emboli. Inhaled $^{14}$O$_2$ rapidly labels pulmonary capillary blood with $^{14}$H$_2$O, which is a useful indicator for measuring blood flow. Studies of regional clearance of $^{14}$O$_2$ in isolated animal-lung preparations have shown that regional clearance of $^{14}$O$_2$ is directly proportional to regional pulmonary blood flow (2,3). In the present study, regional clearance of $^{14}$O$_2$ was markedly delayed in pulmonary segments occluded by emboli, and improved following 1 wk of anticoagulant therapy. Thus, $^{14}$O$_2$ imaging, performed sequentially, permits evaluation of changes in regional blood flow rates to embolized pulmonary segments during anticoagulant treatment, and permits assessment of changes in the size of perfusion defects caused by emboli.

In a previous study of experimentally induced pulmonary emboli in anesthetized dogs (6), we demonstrated the feasibility of using repeated $^{14}$O$_2$ imaging to follow the resolution rates of autologous emboli. Barium-impregnated blood clots were carried to the lungs and located radiographically and by $^{14}$O$_2$ imaging. Clots ranging from 2 to 5 mm in diameter consistently disappeared within 24 hr, with corresponding disappearance of associated focal zones of retained $^{14}$O$_2$. The rapid fibrinolysis of autologous blood clot emboli in dogs was also observed in earlier experimental studies (13,14).

Previous radionuclide and contrast angiographic studies of the resolution rates of pulmonary emboli in patients during heparin therapy have demonstrated highly variable individual rates of improvement (15,16). Recent studies have shown, however, that improvement occurs relatively rapidly. In the Urokinase Pulmonary Embolism Trial, repeat pulmonary angiograms 24 hr after initiation of heparin therapy demonstrated an average decrease of about 20% in the degree of embolic obstruction previously
documented angiographically (17). Other angiographic studies have shown that partial resolution is common (16,17), and complete resolution may occur (18), after only 1 wk of anticoagulation therapy. Although the number of patients studied in the present investigation was small, we observed that younger patients tended to experience more rapid resolution of emboli than elderly patients. This is in agreement with a similar finding reported in the Urokinase Pulmonary Embolism Trial (17).

Although performing C14O2 imaging is technically simple, the inhaled C14O2 must be completely distributed throughout both lung fields to avoid missing emboli in poorly ventilated segments. Occasionally, patients with pleuritic chest pain experience difficulty inspiring deeply. We have found two technical modifications useful for assuring complete distribution of inhaled C14O2. First, the C14O2 should be diluted in a sufficiently large volume of air to permit deep inspiration. Second, for certain patients two or even three deep inspirations of C14O2 from an anesthesia bag are necessary to disperse the C14O2 adequately to the lung bases.

CONCLUSION

In summary, the present study demonstrates the feasibility of serial positron imaging of inhaled C14O2 for the assessment of resolution rates of pulmonary emboli during anticoagulant therapy. Detection of emboli by C14O2 imaging is rapid, sensitive, and specific, and the technique can be performed repeatedly owing to the short half-life of O-15 and its reduction of radiation exposure. Repeat C14O2 inhalation imaging permits sequential evaluation of changes in regional pulmonary blood flow and changes in the size of perfusion defects during anticoagulant treatment. The present preliminary trial suggests that partial resolution of emboli is common after 1 wk of anticoagulation therapy and that complete resolution may occur that early. Further observations regarding changes in blood flow and perfusion defects with time during anticoagulation will require study of larger numbers of patients, with serial C14O2 imaging at more frequent intervals.

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FOOTNOTE

* Holter Model 913, New York, NY

REFERENCES