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# Imaging Small Pulmonary Ischemic Lesions after Radioactive Carbon Monoxide Inhalation

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***A new method is described for imaging small ischemic regions in the lung immediately after a single breath of radioactive carbon monoxide ($^{11}CO$). A tungsten-collimated scintillation camera is used to visualize the 0.51-MeV annihilation photons due to the $^{11}C$. In normal dogs the entire field is cleared of $^{11}CO$ within 10 sec. However, in dogs with experimentally occluded 2-mm-diam segmental arteries, the ischemic but well-ventilated segment appears as a region of persistent high radioactivity, due most likely to temporary entrapment of $^{11}CO$-labeled red blood cells in the ischemic region. This technique also provides a simple noninvasive means for instantly labeling the systemic circulation without left heart catheterization.***

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No method for visualizing *regional* impairment of carbon monoxide transport has been reported to date. Current procedures using nonradioactive carbon monoxide ($D_{CO}$) measure overall or integrated abnormalities, but they cannot indicate localized disease (*1*).

This preliminary report describes the principles and technique of a new inhalation lung-imaging procedure for detecting impaired CO transport on a regional basis. In the near future, this method will be practical in hospitals having a medical cyclotron capable of producing the positron-emitting carbon monoxides $^{11}CO$ or $C^{15}O$. The procedure uses a scintillation camera, equipped with a tungsten collimator with thick septal walls to handle the 0.51-MeV photons, or preferably a computerized positron-emission transaxial tomograph (*2*). Our initial studies with experimental pulmonary arterial occlusion in dogs suggest that a major clinical application of the $^{11}CO$ inhalation lung-imaging procedure may be the visualization of "hot" ischemic lesions produced by small pulmonary emboli not currently detectable by radionuclide ventilation–perfusion imaging or by selective pulmonary arteriography.

## PRINCIPLES AND BACKGROUND DATA

Carbon monoxide gas is known to diffuse rapidly across the normal alveolar–capillary membrane. It has an extremely high affinity for the hemoglobin in circulating red blood cells (210 times that of $O_2$) and forms a stable compound, carboxyhemoglobin, which remains in the blood for several hours or longer, depending upon the initial concentration (*3*). Various diseases of the lungs produce regions where the airways are patent, vascular perfusion is normal, but the alveolar membrane is thickened, which results in a much slower diffusion of gases through the diseased regions than in surrounding healthy tissue. Within a few seconds after a single breath of radioactive carbon monoxide, the diseased areas with thickened membranes should contain high radioactivity levels compared with the normal surrounding lung (Table 1).

In 1968, attempts were made to demonstrate this principle by studying the pulmonary distribution of radioactivity after the inhalation of various radioactive aerosols with different solubilities and absorption rates across the alveolar membrane. The most promising agents for this purpose were aerosols of $^{99m}$Tc-pertechnetate and $^{99m}$Tc-DTPA. Trial studies

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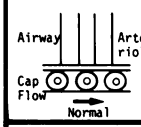
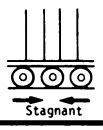
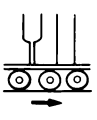
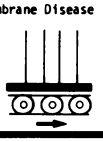
were made in a patient with pulmonary alveolar proteinosis, but no patients with pulmonary embolism were investigated. The findings were inconclusive and the project was discontinued pending the availability of radioactive gases (*4*).

In acute pulmonary embolism without infarction, the ischemic region remains normally ventilated in nearly all patients (*5,6*), while the blood in the alveolar–capillary network is presumably stagnant. Therefore, a single inhalation of $^{11}CO$ gas should fill the entire lung instantly with the radioactive gas. In both the normal lung and the ischemic but well-ventilated lung, radioactive carbon monoxide should traverse the alveolar membrane and combine with the hemoglobin of the circulating red cells almost instantly. These $^{11}CO$-labeled cells should be cleared within seconds from normal lung tissue but will be temporarily trapped in ischemic regions. Subsequently, the trapped labeled cells should clear at relatively slow rates, probably by way of the nutrient bronchial circulation, which remains functionally intact. The experiments reported here were intended to test this hypothesis (Table 1) and to show the capability of the $^{11}CO$ imaging procedure to display the small ischemic lesions produced by minute emboli as "bright lights in the dark."

**TABLE 1. PREDICTED RESULTS OF PULMONARY VENTILATION–PERFUSION–DIFFUSION IMAGING, COMPARED WITH STANDARD FINDINGS WITH STABLE CO IN VARIOUS DISEASE STATES**

| Classification | Lung Imaging Findings | | | Standard |
|---|---|---|---|---|
| | Ventilation | Perfusion | Diffusion | $D_{CO}$ Results |
| Normal Subjects   | Even Distribution and Washout | Even Distribution Normal Gradient Top-Bottom | Lung clears of $^{11}CO$ or $C^{15}O$ within one minute | Normal Values |
| Pulmonary Embolism   | Even Distribution and Washout | Regional Ischemia | Prolonged $^{11}CO$ or $C^{15}O$ Retention in Ischemic regions only | Normal or Impaired |
| COPD  | Uneven Distribution & Regional Air Trapping | Normal or Regional Ischemia | Normal or * Areas of Prolonged $^{11}CO$ or $C^{15}O$ retention | Normal or Impaired |
| Membrane Disease  | Even Distribution and Washout | Normal | General or * Regional Prolonged $^{11}CO$ or $C^{15}O$ Retention | Normal or Impaired |

*
1) Diffusion procedures done only in normal dogs and human subjects and in dogs with pulmonary arterial occlusion. Diffusion findings are presumed, not proved, in COPD and in primary membrane disease.
2) Ventilation/perfusion lung imaging has been done in thousands of patients with PE and COPD.

## MATERIALS AND METHODS

The scintigraphic equipment used in these studies consisted of a Searle Radiographics Pho/Gamma III HP camera, fitted with a tungsten collimator* for imaging the 0.51-MeV annihilation photons of $^{11}C$, and a Picker Model 2C scintillation camera for examinations of ventilation and perfusion with $^{133}Xe$ gas and $^{99m}Tc$-macroaggregated albumin ($^{99m}Tc$-MAA), respectively. The data from the Pho/Gamma camera were recorded on magnetic tape for replay and computer analysis of the counting rates from selected areas of interest.

**Preparation of $^{11}CO$ and $C^{15}O$.** The $^{11}CO$ gas was produced by the $^{14}N(p,\alpha)^{11}C$ reaction by bombarding nitrogen gas (99.990%) with 14-MeV protons in our biomedical cyclotron. The trace of oxygen in the system was sufficient for conversion of $^{11}C$ activity to carbon monoxide by passing the target gas over zinc powder at 400°C. All detectable radioactivity was in the form of $^{11}CO$, as determined by radioactive gas chromatography. The concentration of nonradioactive "carrier" carbon monoxide was less than 20 parts per million.

Carbon monoxide labeled with $^{15}O$ (half-life, 2 min) was prepared by bombarding nitrogen gas containing 0.1% oxygen with 6.3-MeV deuterons for 8 min. The gas mixture was then passed rapidly over activated charcoal at 975°C, through a dry soda-lime trap to remove unconverted $CO_2$, and finally through a 0.45-$\mu$m membrane filter into a lead-shielded 100-ml gas syringe. The yield was usually 15 mCi per 100 ml of gas.

**Dosimetry.** The radiation dose delivered by a single inhalation of $^{11}CO$ was calculated for various target organs using standard methods (*7–9*). The absorbed radiation doses, in millirads per millicurie of inhaled $^{11}CO$, are: 86 to the heart; 45 to the lungs, liver, and kidneys; 15 to the red marrow; 9 to the ovaries or testes; and 11 to the total body.

The absorbed radiation doses (in mrad/mCi) for inhaled $C^{15}O$ are: heart, 15; lungs, 7; liver, 6; kidneys, 7; red marrow, gonads, and total body, 2 each. These are the upper limits of irradiation; the actual doses are in all likelihood less than these.

**Experimental pulmonary arterial occlusion.** Prior to pulmonary artery catheterization and angiography, inhalation–breath-holding–rebreathing and washout studies were done with $^{133}Xe$ in dogs to determine the patency of the airways and the pulmonary ventilatory capacity. This provided a baseline for the subsequent examinations. After the placement and inflation of a balloon-tipped catheter in a segmental

* Made in our shops according to the design of Paul Harper, University of Chicago Hospital, Chicago, Ill.

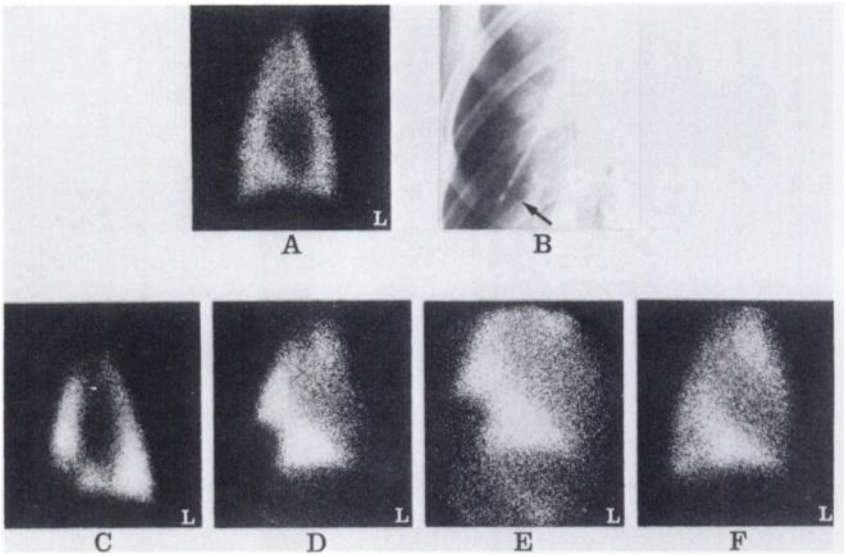



**FIG. 1.** Normal $^{133}$Xe anterior image of lungs (A) during breath-holding (baseline) and chest film (B) showing balloon catheter in segmental pulmonary artery, 2 mm in diameter, supplying right lower lobe. Following inflation of balloon, anterior perfusion image (C) shows defect at right base, best seen in 45° RAO projection (D), and seen equally well with tungsten collimator (E). Ischemic region is ventilatable with $^{133}$Xe gas (F).

artery of the right lung, perfusion images were obtained with $^{99m}$Tc-MAA to verify the existence and location of an ischemic lesion. The camera was then repositioned to give the best visualization of the ischemic segment. A repeat $^{133}$Xe inhalation examination verified the patency of the airway to this segment.

The dog was then placed under the tungsten-collimated Searle Radiographics camera and the right side of the chest was imaged again in the 45° RAO position, using the $^{99m}$Tc window, to compare the spatial resolutions of the low- and the high-energy collimators for $^{99m}$Tc. Three millicuries of $^{11}$CO gas were mixed in 50 ml of 100% oxygen. The mixture was administered during a single inspiration through an endotracheal tube with a two-way valve to permit inhalation and subsequent collection of the exhaled air and unabsorbed $^{11}$CO in a lead-shielded plastic bag. Polaroid pictures were taken during the first 30 sec and then at 2-min intervals for 10 min. The data were stored in the 5407A Hewlett–Packard scintillation data analyzer. At this point, the balloon of the catheter was deflated. After a 110-min waiting period to allow the retained $^{11}$CO to decay (half-life, 20 min), another 3.0 mCi of $^{11}$CO was administered and the right side of the dog's chest was again imaged at the same intervals for 10 min. This second inhalation procedure was done to show that, with a return to normal blood flow in the previously ischemic segment, the $^{11}$CO clears within seconds and at the same rate as from normal surrounding lung. These data were also recorded on tape for subsequent analysis. The perfusion and $^{133}$Xe ventilation lung-imaging procedures were repeated 2 hr after the balloon was deflated to verify the restoration of normal pulmonary arterial blood flow and ventilatory capacity in the right lung.

## RESULTS

The baseline radioxenon lung images showed normal ventilatory function, and a chest roentgenogram showed the tip of the balloon catheter to rest in a 2-mm-diam segmental branch of the right lower lobe (Figs. 1A and 1B). Inflation of the balloon produced a segmental ischemic defect (greatest dimension, 40 mm) without loss of ventilation, best visualized in the 45° RAO projection. Both the Picker Dynacamera, with a 32.5-cm field of view, and the tungsten-collimated Searle Radiographics camera, with a 24-cm field of view, performed adequately (Figs. 1C–1F). Serial lung images taken in the 45° RAO projection over the first 8 min showed that the ischemic segment became and remained an area of relatively high radioactivity, 70 mm in greatest dimension, whereas the rest of the lung was cleared within 10 sec. This relation persisted for nearly 8 min, during which time the region of the heart blood pool became more radioactive (Fig. 2A). Time–activity curves registered from equal-sized areas of normal and ischemic lung and from the heart are shown in Fig. 2B. The same procedure was repeated after deflating the balloon. Again the lungs were cleared during the first 10 sec, but the previously ischemic segment failed to show a persistent high level of radioactivity, while an area of relatively high radioactivity again appeared in the region of the heart blood pool.

## DISCUSSION

**Selection of radioactive tracers.** The $^{11}$C-carbon monoxide gas is certainly the agent of choice because of its almost instant diffusion across the alveolar membrane in one direction only. Oxygen and carbon dioxide labeled with $^{15}$O diffuse less rapidly and may pass the membrane in both directions. All

of these gases are cyclotron-produced positron-emitters. When positrons and electrons collide, 0.51-MeV annihilation photons are released. This high-energy radiation is detectable with standard scintillation cameras, but at a lower efficiency than the less energetic photons from $^{99}$Tc (140 keV) and $^{123}$I (159 keV). Other radioactive gases such as $^{133}$Xe and $^{85}$Kr are not suitable because they are poorly soluble in watery fluids and their passage into the circulation is relatively slow and inefficient. Thus, $^{11}$CO combines the longer half-life of $^{11}$C (20 min vs. 2 min for $^{15}$O) with the desirable diffusion and chemical properties of CO.

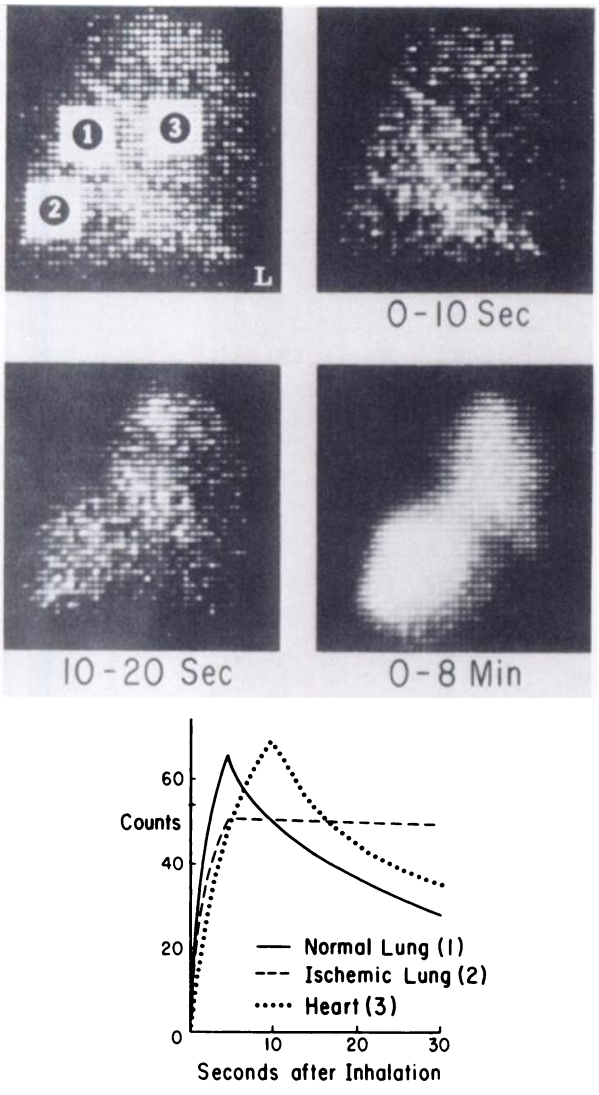



**FIG. 2.** (Top) Lung images taken in RAO projection immediately after single inhalation of $^{11}$CO gas. Areas of interest are located over normal (1) and ischemic (2) lung and heart (3). Ischemic lung region becomes and remains highly radioactive, compared with normal lung (10–20 sec), while activity levels in heart blood pool and ischemic lung increase in 0–8-min integrated image. (Bottom) Normal and ischemic lung curves reach peaks at 5 sec, but ischemic lung remains at high plateau, while normal lung curve descends. Curve for heart blood pool peaks at 10 sec.

The $^{11}$CO gas used in these investigations was chemically pure. The amount of carrier carbon monoxide in a 10-mCi dose in 50 ml of nitrogen is at most one-hundredth the quantity used in standard single-breath and short rebreathing procedures. The radiation exposure per test is well within acceptable limits.

**Significance of $^{11}$CO lung images.** The ability to relate abnormal $D_{CO}$ values to localized disease may add an important new dimension in the diagnosis and management of such major pulmonary disorders as pulmonary embolism, chronic obstructive pulmonary disease (COPD), and other disorders involving the alveolar membranes. The *regional* pulmonary $^{11}$CO diffusion procedure, used in conjunction with conventional ventilation–perfusion lung imaging, may allow accurate assessment of the abnormal nonradioactive $D_{CO}$ values found in all of these diseases (Table 1). Specifically, with the three lung-imaging procedures one might be able to distinguish regional airway obstruction, with or without perfusion defects, from alveolar membrane disease. Studies of patients using the triple procedure are being initiated. Since the $^{11}$CO diffusion procedure provides qualitative data only, both on a regional and on an overall basis, it will be necessary to correlate $^{11}$CO lung-imaging data with quantitative values of nonradioactive $D_{CO}$ measurements. However, with computer analysis of tape-recorded data from selected areas of interest, one can compare the blood clearance rates from normal and abnormal regions of the lung. For example, Fig. 2B shows the sluggish clearance of $^{11}$C-labeled red blood cells from an ischemic segment of a dog lung, compared with the rapid clearance from a healthy segment.

**Diagnostic advantages in pulmonary embolism.** For detecting small pulmonary emboli, the $^{11}$CO lung-imaging procedure should allow visualization of an ischemic lesion supplied by pulmonary arterioles 150–200 $\mu$m or less in diameter. This considerable increase in sensitivity is predictable from the pulmonary artery occlusion data shown in Fig. 3. Here the balloon-tipped catheter occluded a 2-mm segmental artery to the right lower lung. In the routine $^{99m}$Tc-MAA perfusion lung image the region of ischemia was manifested as an area of low radioactivity (40 mm in greatest dimension) surrounded by a high-activity field. After $^{11}$CO inhalation, this same ischemic region appeared as an area of relatively high radioactivity (maximum dimension, 70 mm) surrounded by a field of practically no radioactivity. There is at least a 20-fold difference between the size of the vessel occluded and that of the ischemic lesion produced. Thus, there should be at least a 10-fold increase in sensitivity because a "hot"

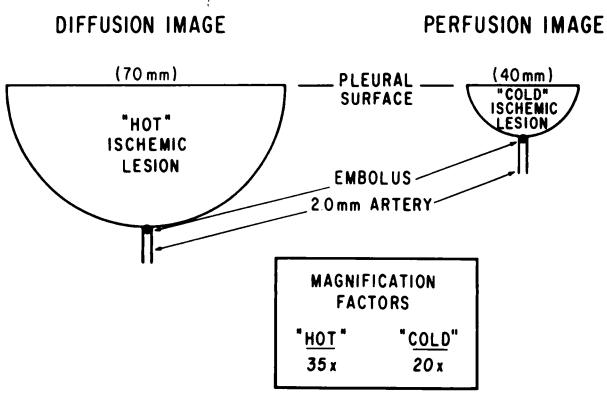



**FIG. 3.** Size of image obtained by $^{11}CO$ diffusion compared with that of $^{99m}Tc$-MAA perfusion lung image, as produced by occlusion of 2-mm pulmonary artery. Magnification factors of 35 and 20, respectively, are illustrated.

lesion in a "cold" field is found to be considerably larger than the "cold" lesion in the "hot" field when both are produced by occlusion of an artery of the same size. Another factor that should contribute to the greater sensitivity of visualizing "hot" lesions in "cold" fields is the fact that "hot" lesions as small as 2–3 mm in diameter produce images several times larger depending upon the resolving power of the imaging equipment used. With our Picker Model 2C Dynacamera and a medium-energy collimator, the resolution at a depth of 3 in. in lung tissue is approximately 12 mm. Thus, all "hot" lesions of 2–10 mm diameter, having target-to-background ratios exceeding 5, may appear to have the same diameter (12 mm).

With this capability, microemboli should be detectable, whereas at present a definitive diagnosis of this disease can be achieved only by open lung biopsy (*10*). By contrast, the carbon monoxide procedure requires only a single inhalation of gas, and the small ischemic lesion may be located and detected by a completely noninvasive safe rapid technique that requires minimal patient cooperation. The radiation exposure to the lungs, blood, and whole body fall well within accepted limits set by the federal regulatory agencies. Specifically, the calculated radiation dose to the lung from inhaling $^{11}CO$ is 45 mrad/mCi, considerably less than that received from pulmonary arteriography used to confirm the diagnosis of pulmonary embolism.

**Limitations in other pulmonary disorders.** Although the $^{11}CO$ lung-imaging procedure indicates no alteration in the one-way alveolar–capillary membrane transport in acute experimental embolism and in normal dog lung, it remains to be seen whether a thickened membrane, in the absence of any perfusion defect, can produce scintigraphic evidence of regional impairment of $^{11}CO$ transport. The gas might be exhaled before an area of abnormally high concentration could be detected. Moreover, the gas could pass through collateral alveoli and bypass the regions with thickened membranes. On the other hand, in small-airway obstructive disease, the inhaled $^{11}CO$ might penetrate to the alveoli in relatively small amounts, while the bulk of the inhaled gas could be trapped in the terminal airways. Under these circumstances, as in alpha$_1$-antitrypsin-deficiency emphysema, there might be excessive regional $^{11}CO$ retention as well as $^{133}Xe$ retention during the washout phase, but the retention of xenon would probably be greater than that of carbon monoxide because of their greatly different rates of diffusion.

**Potential nonpulmonary applications.** Based on the same principle involved in detecting ischemic pulmonary lesions, as areas containing relatively high levels of $^{11}CO$-labeled hemoglobin in stagnant pools of red blood cells, numerous possible applications are apparent. An inhalation of $^{11}CO$ or $C^{15}O$ instantly labels the red cells in the systemic circulation to every organ and tissue in the body. Therefore, regional impairment of the arterial blood supply to any organ should appear as a region of reduced radioactivity during the first pass through the organ. Thereby, the effects of acute embolism or infarction should be apparent within the first 10–20 sec after a single inhalation of radioactive CO. Infarcts of the brain, lung, liver, spleen, kidney, and extremities should show regions of relatively reduced radioactivity during the first passage of systemic arterial blood through the organ. In addition, regional impairment of venous blood flow from the same areas should be detectable as regions of relatively high radioactivity levels, provided there is temporary entrapment of red blood cells such as in thrombophlebitis of the lower extremities and pelvis and in venous occlusive diseases of the liver (Budd–Chiari syndrome), kidney, brain, and other organs.

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