Ventilation-Perfusion Lung Imaging and Selective Pulmonary Angiography in Dogs with Experimental Pulmonary Embolism


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To determine the accuracy and limitations of Xe-133 ventilation and Tc-99m perfusion lung images (V-P images) in detecting pulmonary emboli (PE), these studies were performed in 23 dogs after experimental production of PE by a modified Wessler technique. Fourteen of the animals also underwent selective pulmonary angiography. Xenon-133 abnormalities were seen immediately after embolization in two of the 23 animals (8.7%). Perfusion images revealed the location of 83% of emboli that completely obstructed pulmonary vessels, but only 26% of those that partially obstructed flow. Defects were seen with 97% of emboli that completely occluded vessels larger than 2.0 mm in diameter, but in only 66% of those occluding smaller vessels. Oblique perfusion images provided the only evidence of the perfusion defect associated with five of 88 (5.7%) angiographically proven emboli. V-P imaging is a sensitive technique for detecting PE unless the emboli lodge in very small vessels or incompletely obstruct a vessel. Xenon-133 abnormalities occur infrequently following PE, and should not be a common cause for a false-negative V-P match in clinical practice.


Perfusion lung scanning, first introduced in 1964 (1,2) remains an important noninvasive test for the diagnosis of pulmonary embolism. The sensitivity of the test has been improved in recent years by the use of Tc-99m-labeled lung agents and better imaging instruments, and the specificity of the test has been improved by performing ventilation studies (usually with Xe-133 gas) in conjunction with perfusion images (3–5).

Several years ago Moser et al. (6) compared the results of perfusion lung scans and pulmonary angiography in dogs with experimentally produced pulmonary emboli. In that study, macroaggregated albumin (MAA), labeled with I-131 or Tc-99m was used to obtain four-view lung scans, and pulmonary angiograms were performed by injecting contrast media into the main pulmonary artery or the right atrium. One goal of the current study was to re-evaluate the sensitivity of lung scanning and pulmonary angiography in the detection of emboli. Another goal was to determine the accuracy of perfusion images in detecting emboli that partially obstructed pulmonary vessels.

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nary angiography by comparing Tc-99m MAA perfusion images—which included four standard views and four oblique projections (two anterior, two posterior obliques)—with the results of angiography performed by selectively injecting the right and left pulmonary arteries.

This study also provided an opportunity to investigate the occurrence of Xe-133-detectable abnormalities of the airways induced by pulmonary emboli. Emboli are known to cause bronchospasm in animals (7—9), but these effects are reported to be immediate and transient. Similar bronchospasm apparently occurs in man and may be detected by Xe-133 imaging (10,11), causing a false-negative ventilation-perfusion (V-P) match in patients with pulmonary emboli. In the current study this phenomenon was investigated by performing Xe-133 washin-washout studies shortly after thromboemboli formed in vivo were released to the lungs.

Methods

Xenon-133 ventilation images and Tc-99m perfusion lung scans were performed in 23 beagle dogs (10—15 kg) after experimental induction of pulmonary thromboemboli. Each animal was anesthetized throughout the experimental procedure using intravenous pentobarbital (30 mg/kg). This resulted in an unconscious, but spontaneously breathing animal. Each dog initially had a baseline ventilation-perfusion (V-P) radionuclide study to establish normality, the baseline studies being performed within 1 wk of the experimental study. On the day of the experiment, pulmonary thromboemboli were produced in vivo by a modification of the technique of Wessler et al. (12,13). Each intubated, anesthetized animal was placed supine on a small operating table, and cutdowns were performed on the right and left external jugular veins. Each vein was dissected free and a 3 cm segment was isolated using vascular clamps. Using a tuberculin syringe fitted with a 25-gauge needle, 50—100 NIH units of human thrombin were injected into each isolated vein segment. The isolated segment was then gently compressed to disperse the thrombin. After a 20-min waiting period the vascular clamps were removed and the thrombi were released to the lungs. This procedure was performed twice in each animal.

Immediately after embolization the animal was placed prone beneath a gamma camera fitted with a high-resolution, parallel-hole collimator. When these images had been completed, the animal was placed supine and 10 cc of indelible commercial grade India ink* in 10 cc water was injected through the external jugular vein. Somlethol (80 mg/kg) was injected intravenously 1 min after the India ink. The total time from embolization to death was 2.5—3.0 hr in the 14 animals having angiography and 1.0—1.5 hr in the others.

Each animal’s chest was opened immediately after death and the lungs pigmented with India ink were removed. A tube was placed in the trachea and 10% buffered formalin was introduced into the bronchial tree by gravity feed until the lungs were inflated to their normal size. The lungs were photographed and then placed in a large formalin-filled glass container and stored in a lead-shielded area. The next day the lungs were visually examined and any portions not pigmented (i.e., “perfusion defects”) were noted and their length and width measured. Preliminary experiments had demonstrated no change in defect size during the first 24 hr postmortem.) The lungs were then returned to the formalin-filled containers for at least 1 wk of additional fixation. The pulmonary vascular tree was then dissected and the sites and size of thrombi were noted. Only adherent clots were considered to be antemortem.

To further validate the India-ink model, four control dogs had V-P imaging studies and India ink absorber. After an 8-min period of washin, the animal breathed room air (washout). During the Xe-133 study digital data were collected at 5-sec intervals using a small laboratory computer. A single 200,000-count polaroid image of washin, and sequential (1/min) washout images were also obtained.

Immediately after the ventilation study, 14 of the animals were transferred to the angiography suite. After a preliminary film of the chest had been taken, a 6 Fr NIH catheter was introduced through the axillary vein and 20 cc of Renografin-76 was rapidly injected (10 cc/sec) selectively into the right and left main pulmonary arteries. The angiograms were performed with the animal in the lateral position, using 2:1 magnification and a tube with a 0.2-mm focal spot. Breathing was suspended at maximum inspiration during filming by hyperventilating the animal just before contrast injection.

Immediately following angiography (n = 14) or the ventilation study alone (n = 9), an i.v. injection of 2—3 mCi of Tc-99m macroaggregated albumin (MAA) was made. Eight 400,000 count perfusion lung images (including anterior and posterior obliques) were then recorded on Polaroid film using a gamma camera fitted with a high-resolution, parallel-hole collimator. When these images had been completed, the animal was placed supine and 10 cc of indelible commercial grade India ink* in 10 cc water was injected through the external jugular vein. Somlethol (80 mg/kg) was injected intravenously 1 min after the India ink. The total time from embolization to death was 2.5—3.0 hr in the 14 animals having angiography and 1.0—1.5 hr in the others.

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To further validate the India-ink model, four control dogs had V-P imaging studies and India ink
before death. None of these dogs received pulmonary emboli, but two did undergo selective pulmonary angiography. In addition, tissue sections (n = 18) were taken from both pigmented and nonpigmented areas of the lungs of three dogs who did receive pulmonary emboli. These specimens were weighed and counted in a standard gamma well counter to determine their relative activity (cpm/g). Sections of pigmented portions of lung were taken and prepared for routine microscopic examination. The sections were stained with hematoxylin and eosin and the location of the India-ink particles was determined.

During data analysis the perfusion lung images and angiograms were interpreted independently. If an equivocal perfusion abnormality was present which suggested an anatomic variant, the pre-embolic control images of the dog were compared with the post-emboli images and a decision (PE, no PE) was made. This happened infrequently and usually involved findings in the relatively thin canine upper lobes. When a filling defect or sharp cut-off was seen by angiograph, the diameter of the obstructed vessel was measured (corrected for magnification) at the site of the thrombus. The Xe-133 images were interpreted without knowledge of the perfusion or angiographic results. India-ink and pathologic results, which had been tabulated as each study was performed, were referred to only after the other independent analysis had been completed. Throughout the study the lobar anatomy was described by each investigator using terminology applied to human lungs. Thus the upper lobes corresponded to the canine apical lobes; the lower lobes to the diaphragmatic lobes; the right middle lobe to the right intermediate and cardiac lobe; and the lingula to the left cardiac lobe. Statistical analyses were performed using the chi-square test.

RESULTS

Pulmonary thromboemboli were documented by angiography and/or pathologic examination in each of the 23 animals. The average number of segments involved was 5.9 (range 3–10). Pulmonary vessels as small as 1 mm and as large 8 mm in diameter (lobar vessels) were occluded, but most of the emboli lodged in subsegmental vessels 2–5 mm in diameter. The right and left lungs were embolized with roughly equal frequency (70 emboli on left side, 66 on right). The lower lobes contained two-thirds of all emboli, with the posterior and lateral segments being the most frequent sites of embolization within the lower lobes.

India-ink lung preparations revealed defects in all but two of the segments containing documented emboli. The reason for the discrepancy in these two instances was unclear. In control animals who did not undergo angiography, India ink blackened the lungs uniformly. In two control animals that did have angiography, infrequent small (<2 × 2 cm) pink zones were present (the perfusion images of these two dogs were normal). Accordingly, small post-angiographic India-ink defects not associated with angiographic or pathologically proven emboli were disregarded during the subsequent data analysis. In animals with emboli, sections from central portions of lung blackened by India ink (n = 7) showed much higher average cpm/g than central portions from pink sections (n = 7) distal to emboli. The count ratios ranged from 27:1 to 220:1 (mean ratio 108:1). Tissue sections (n = 4) comparing the ratio (cpm/gm) across border zones between pigmented and non-pigmented tissue revealed 15:1 higher cpm/gm on the pigmented side of the border. When the blackened sections of lung were examined histologically, most pigment particles were found free within the lumen of alveolar capillaries. An occasional particle was found within a pulmonary macrophage.

The size of the surface India-ink perfusion defect created by an embolus was closely related to the ability of the perfusion image to detect the embolus. Only eight of 28 (29%) angiographically proven emboli associated with India ink surface defects smaller than 2 × 2 cm were visualized by scan. The smallest defect seen by scan measured 2 × 0.5 cm on the lung surface. Fifty-four of 60 angiographically proven emboli (90%) associated with surface defects larger than 2 × 2 cm were visualized by scan (p < 0.001).

Emboli completely occluded pulmonary vessels 69 times in the 14 dogs undergoing angiography. Fifty-seven of these emboli (83%) created perfusion defects that were visible in perfusion scans (Fig. 1). The detection rate for emboli completely occluding vessels larger than 1.0 mm in diameter was 90% (54/60), but only 33% of emboli occluding vessels less than 1.0 mm in diameter were detected (Table 1). Detection was significantly (p < 0.001) less likely if the thrombus only partially occluded a vessel. Only five of 19 (26%) incompletely obstructing thrombi seen angiographically were detected by the perfusion images (Fig. 1). The possibility that poor detection was associated with the anatomic site of the emboli (e.g., upper vs. lower lobe) was assessed by tabulating the location of the 12 completely obstructing emboli that were undetected by perfusion imaging. Five of these emboli were in upper lobes, four were in the right middle lobe or lingula, and three were in the lower lobes. Only three pathologically proven emboli were not detected by
FIG. 1. Selected images from control and postembolism perfusion scans (A), the pulmonary angiogram (B), and India-ink preparation, RPO view (C) and LPO view (D) are shown. Correspondence between perfusion defects, emboli (arrows), and India ink defects is seen. Perfusion defects are present in left apex, lingula, lateral and superior segments of left lower lobe, posterior segment of right base and periphery of right upper lobe. By scan there is no perfusion defect in anterior segment of lower lobe. Angiogram shows partially obstructing embolus in that segment (white arrow). Perfused lung appears black in India-ink images, perfusion defects are gray. White nonsegmental areas are reflected light and should be disregarded.

selective angiography; all were in 1-mm vessels. One of these emboli was associated with a positive perfusion scan.

Comparison of oblique perfusion images with the four standard perfusion views was possible in 21 animals (two animals had technically unsatisfactory
showed, in four dogs, that there was "negligible" I-131 MAA activity in nonpigmented sections of lung following embolization. The activity ratios between pigmented and nonpigmented zones in the current study confirm and extend their findings. Levy also stated that nonstained lung occurred only in segments containing emboli. The current results demonstrate that small nonpigmented areas can occur in control animals after selective angiography, in the absence of pulmonary emboli. Thus, when angiography is used, the India-ink model requires pathologic confirmation to determine the presence and location of emboli. If angiography is not employed, the model seems valid per se, as an India ink defect (regardless of etiology) represents a perfusion deficit which might be detected during perfusion imaging. The use of India ink as a perfusion marker also minimizes the potential problem of positional alterations of emboli after angiography. The close correlation between angiographic, pathologic, and India ink localization of emboli suggests that significant positional changes did not occur after angiography in this study.

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<tr>
<th>Angiographic size of vessel occluded</th>
<th>Visualized in lung scan</th>
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<tbody>
<tr>
<td>&lt;1.0 mm</td>
<td>9</td>
</tr>
<tr>
<td>1.1–2.0 mm</td>
<td>23</td>
</tr>
<tr>
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<tr>
<td>&gt;3.0 mm</td>
<td>24</td>
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<tr>
<td>Total</td>
<td>69</td>
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* Data in this table concern only emboli that completely occluded pulmonary vessels.

oblique views). Oblique images provided the only evidence of the perfusion defect associated with six emboli (five animals) (Fig. 2). These defects involved the lateral segment of a lower lobe (revealed by a posterior oblique view) in four instances and the apical segment of an upper lobe (revealed by an anterior oblique) in two. None of these lesions was smaller than 2 × 2 cm at the surface, as measured from the India-ink preparation. Five of these emboli occurred in animals who underwent angiography. Thus five of 88 (5.7%) angiographically proven emboli were detected only by oblique perfusion images. In eight other animals, oblique views provided the best visualization and/or localization of lesions (n = 10) that were seen on standard views. Visualization of defects in the lingula, right middle lobe, and lateral segments of the lower lobes was improved by posterior obliques. In one instance, a right anterior oblique view improved visualization of a lingular defect. Eight of these emboli were angiographically proven. Thus oblique views provided the only evidence (n = 5) or best visualization (n = 8) of perfusion defects associated with 13 of the 88 (14.8%) angiographically proven emboli.

There was no abnormal Xe-133 washout retention in the 23 animals studied. However, two animals (8.7%) did show Xe-133 defects in their equilibrium images that were not present in their control Xe-133 studies. Both these animals showed deficient Xe-133 activity in a lower lobe that contained an embolus completely obstructing a large (6–8 mm diam), proximal lower-lobe vessel (Fig. 3). Only these two emboli, which represent 1.5% of the total 136 emboli, were associated with Xe-133 abnormalities.

**TABLE 1. LUNG SCAN VISUALIZATION OF ANGIographically PROVEN PULMONARY EMBOLI***

**FIG. 2.** Selected control and postembolism perfusion images from one animal's study are shown. Perfusion defect in lateral segment of right lower lobe was seen only on oblique view (arrow).
The results of the current study demonstrate that perfusion lung imaging is a sensitive detector of perfusion defects caused by pulmonary emboli. Moser (6,14) previously stated, from studies of a thorax-lung phantom, that perfusion defects measuring less than 2 in. at the lung surface were rarely detected by scans. In the current study, surface defects larger than 2 x 2 cm (roughly 0.75 in. on edge) were readily detected (90%). The improvement noted is probably the result of the resolving power of improved imaging instruments. The ability of the perfusion image to reveal a perfusion defect was primarily related to the size of the vessel obstructed and the completeness of the obstruction. The anatomic location of emboli did not seem important, though the thinness of the upper lobes in dogs made confident assessment of this area more difficult. Potential interpretative difficulties were minimized by referring to control pre-embolic images.

The sensitivity of lung imaging in the current study was improved by the use of oblique views. These were suggested as a complement to the standard four-view lung scan several years ago (15,16), and Caride et al. (17) recently recommended that posterior oblique images be a routine part of a perfusion lung examination. Their study showed that more perfusion defects were seen when oblique views were added to the four standard views. There was no angiographic confirmation of emboli in their study, but the results suggested that oblique images would be helpful in detecting emboli. In the current study, the utility of the oblique view in detecting PE has been demonstrated. The posterior oblique views were helpful more often than the anterior obliques, but this may be related partly to the supine position of the animals during embolization, which favors posterior deposition of emboli.

Moser et al. (6) stated that “standard” angiography (defined as performed by injection of the right atrium or the main pulmonary artery) was not able to detect small, peripheral clots. The current study shows that selective injection of contrast into the right or left pulmonary artery of dogs results in detection of clots in vessels as small as 1 mm in diameter. Only three pathologically proven thrombi (all in 1-mm vessels) were not detected by angiography. It should be noted, however, that the angiography was performed under nearly ideal technical conditions (i.e., near-maximum efficiency would be expected). Segmental injections of contrast (18), which might have further increased the sensitivity of the angiogram, were not performed in this study.

The sensitivity of the perfusion images performed in the current study was excellent, but some laboratories have equipment that might allow further improvements. The perfusion images in the current study were performed using a 19 photomultiplier HP-grade camera fitted with a high resolution parallel-hole collimator. The newer 37-PMT large-crystal cameras have better imaging capabilities (19), and allow parallel-hole collimators to be used for lung perfusion imaging in patients. In addition, the sensitivity of the perfusion images might have been improved by minimizing the adverse effects of res-
riratory motion on image quality. This could be done either by imaging the lungs only during the end-inspiratory phase ("respiratory gating") or imaging the moving lungs throughout the respiratory cycle and displaying the study in cinematic format (20).

The limited specificity of perfusion-scan defects is also an important problem when radionuclide lung imaging is employed in clinical practice (21). Ventilation lung imaging with Xe-133, performed as part of a combined ventilation-perfusion study, allows emboli to be diagnosed as areas of abnormal perfusion and normal ventilation (V-P mismatch). This approach has been shown to increase the specificity and accuracy of perfusion imaging (5). Unfortunately, pulmonary emboli have been implicated as a cause of regional bronchoconstriction in patients (22–24), and recent case reports (10,11) suggest that this bronchoconstriction may result in abnormal Xe-133 studies in man. If this occurred commonly, it could be an important cause for false-negative Xe-i 33 studies in man. If this occurred commonly, it could be an important cause for false-negative ventilation-perfusion matching in patients with PE.

Studies in dogs indicate that bronchoconstriction occurs following the deposition of autologous pulmonary thromboemboli (25,26) or the occlusion of pulmonary vessels by balloons or other foreign-objects (27,28). These studies conclude that the phenomenon occurs immediately upon occlusion of the vessel but is transient, persisting no longer than 6–8 hr. Thomas et al. (29) suggested that platelets adhere to fresh autologous thromboemboli and release amines that induce this bronchospasm in patients. In the current study fresh autologous thrombi were produced and released to the lung to simulate, as closely as possible, the situation in a patient with PE. Xenon-133 imaging was begun within minutes of the final embolization to maximize the probability of detecting this immediate, transient bronchoconstriction. Even under these circumstances, ventilation abnormalities were infrequent (9% of animals, 1.5% of emboli) in the postembolic period.

Wolfe and Sabiston (26) suggested that ventilation abnormalities seen by imaging were associated with complete occlusion of the pulmonary artery or a proximal, major arterial branch. Their hypothesis is supported by the fact that the only two emboli associated with ventilation changes in the current study were large, proximal clots obstructing vessels 6–8 mm in diameter, supplying the major portion of a lower lobe. Smaller clots were not associated with Xe-133 abnormalities. Whether ventilation changes (a) did not occur secondary to the smaller emboli, (b) did occur but had disappeared before the ventilation study, or (c) were present but involved small areas that were undetectable, is not clear. The infrequent occurrence of ventilation abnormalities seen in this animal study suggests that bronchospasm induced by emboli is unlikely to be a common cause of false-negative ventilation-perfusion match in clinical practice.

ACKNOWLEDGMENT

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Research was conducted according to the principles enunciated in the "Guide for the Care and Use of Laboratory Animals," prepared by the Institute of Laboratory Animal Resources, National Research Council.

FOOTNOTE

* Pelican Drawing Ink, Gunther-Wagner, 17-Black Indelible.

REFERENCES


15. Wellman HN, Mack JF, Saenger EL, et al: Clinical experience with oblique views in pulmonary perfusion scin-


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P. O. Alderson, J. L. Doppman, S. S. Diamond, K. G. Mendenhall, E. L. Barron and Mary Girton