Regional Comparison of Technetium-99m DTPA Aerosol and Radioactive Gas Ventilation (Xenon and Krypton) Studies in Patients with Suspected Pulmonary Embolism

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The regional distribution of [^{99m}Tc]DTPA aerosol was compared with that of ^{133}Xe (n = 30) and krypton (n = 24) in a group of patients with suspected pulmonary embolism. All patients had an aerosol study using a recently available commercial generator system, a ventilation study with one of the gases, and perfusion imaging. Regional information was assessed visually on xenon, krypton, and aerosol studies independently by considering each lung as three equal-sized zones. In addition, gas ventilation findings peripheral to regions of aerosol turbulence ("hot spots") were evaluated. Only 64% of the zones were in complete agreement on xenon and aerosol. Most of the discordance between xenon and aerosol was accounted for by minor degrees of ^{133}Xe washout retention in zones that appeared normal in the aerosol study. An agreement rate of 85% was noted between ^{81m}Kr and aerosol regionally. The regions of discordance between aerosol and gas studies, however, usually were associated with unimpressive perfusion defects that did not change the scintigraphic probability for pulmonary embolism in any patient. Regarding zones of aerosol hyperdeposition, 76% had associated washout abnormalities on xenon; however, there was no correlation between the presence of these abnormalities or perfusion abnormalities. The results confirm the high sensitivity of ^{133}Xe washout imaging, but suggest that radioaerosol imaging will detect most parenchymal abnormalities associated with perfusion defects of significance.

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It is generally accepted that a negative perfusion lung scan excludes the presence of significant pulmonary embolism (PE) (*1,2*). Perfusion abnormalities, however, are too nonspecific to indicate the presence of PE. The combination of appropriate perfusion defects with normal ventilation (i.e., mismatch) in zones of radiographic normality is required (*3*). Unfortunately, there is no ideal technique for assessing the correspondence of ventilation and perfusion in multiple views. Xenon-133 (^{133}Xe) is used in over 90% of the ventilation studies performed in the United States, and its washout phase has been shown to provide sensitive detection of obstructive airways disease (*4,5*). The ^{133}Xe ventilation study has some disadvantages, however, including poor resolution associated with a low photo-peak energy and the fact that only a limited number of views (often only a posterior view) of initial ventilation and washout usually can be performed with a single dose. Krypton-81m (^{81m}Kr) also is used as a ventilation agent (*6,7*), but its high cost has limited its use. Radioaerosols do not have the above-mentioned disadvantages and allow high-quality images in multiple projections with a single administration. Despite the availability of radioaerosols in nuclear medicine for over two decades (*8–12*), they have not gained widespread acceptance. This has been largely because the apparatus used to generate radioaerosols has been cumbersome and has produced aer-

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osols with a wide range of particles sizes. This has resulted in excessive central deposition and relatively poor peripheral penetration of aerosol activity in the lungs. The introduction of a commercially available, government approved, convenient system that produces relatively uniform submicronic particles has led to renewed interest in radioaerosols.

A multicenter clinical study (*13*) involving 107 patients recently demonstrated the abilities of this new form of radioaerosol in the scintigraphic diagnosis of PE. Results from the study showed that radioaerosols had diagnostic equivalence with ^{133}Xe and ^{81m}Kr as an adjunct to perfusion scanning in the diagnosis of PE. However, the following parameters were not evaluated: (a) scintigraphic information on a region-by-region basis, (b) the additional diagnostic contribution of washout assessment with ^{133}Xe, (c) the evaluation of aerosol turbulence (hot spots) and their relationship to findings on gas ventilation studies, and (d) the potential effect of regional discrepancies between aerosol and gas ventilation studies in assigning the final scintigraphic probability of PE. The goals of the current study were to evaluate the above parameters and to further define the clinical merit of radioaerosols in the evaluation of patients with suspected PE.

MATERIALS AND METHODS

Two of the original four centers from the previous prospective multicenter study participated in the current retrospective evaluation. All 30 patients from the original Cedars-Sinai Medical Center (CSMC) population had ^{133}Xe ventilation, aerosol inhalation, and perfusion studies, and all 24 patients from Columbia-Presbyterian Medical Center (CPMC) had ^{81m}Kr, aerosol, and perfusion studies. These patients represent approximately half of those analyzed in the previously reported multicenter study (*13*). This study group consisted of 26 males and 28 females with a mean age of 66 yr (range 20–83 yr). No smoking history was noted in 25, a past smoking history in 16, and an active smoking history in 13 patients. Their studies were reanalyzed to investigate the additional issues mentioned above. The overall probability for pulmonary embolism in this population subset, based on ventilation/perfusion and chest x-ray findings (*13*) was "none" (13%), low (30%), indeterminate (37%), and high (20%).

Imaging Techniques

After giving informed written consent, patients from CSMC had a ^{133}Xe study in the posterior projection after inhalation of 15–20 mCi of ^{133}Xe. A single breath image was followed by a rebreathing phase for 4 min, and that was followed by at least a 5-min washout phase. Next, each patient had a technetium-99m diethylenetriamine pentaacetic acid [^{99m}Tc]DTPA) aerosol inhalation study using the Syntevent aerosol delivery system. Thirty to forty-five millicuries of ^{99m}Tc were placed in the plastic nebulizer along with ~3 ml of sterile saline, and airflow was established through the nebulizer at a rate of 8–10 l/min. The patients breathed the aerosol for 5 min. A six-view aerosol study (ANT, POST, RPO, LPO, RAO, and LAO) was then acquired (100K cts per view). Each view generally required 2–4 min of imaging time. Finally, an eight-view perfusion study (500K cts per view) was performed following injection of 3–4 mCi of [^{99m}Tc]MAA. The patients from CPMC had a six-view aerosol study as described above, followed by ^{81m}Kr images interdigitated with perfusion views. Six ^{81m}Kr views (ANT, POST, RPO, LPO, RAO, and LAO) were obtained (200K cts per view) immediately after the corresponding perfusion image without moving the patient. All the studies at both centers were performed with recent model large-field-of-view scintillation cameras and low-energy all-purpose collimators.

Scintigraphic Scoring System

Scoring of the [^{99m}Tc]DTPA aerosol study, the single breath ^{133}Xe images, the ^{81m}Kr ventilation study, and the perfusion images were performed by arbitrarily dividing each lung into three equal-sized upper, mid, and lower zones. The anterior, posterior, and both posterior oblique views were evaluated visually for scoring aerosol, perfusion, and ^{81m}Kr images. A posterior view single breath image was used for the ^{133}Xe studies. Each of the six zones was graded as "0," "1," or "2"—"0" indicating normal regional activity, "1" indicating a mild deficit or inhomogeneity of activity, and "2" indicating more marked abnormalities of the same type. For the washout phase of the ^{133}Xe study, the following scoring system was used: 0 = normal (no retention of xenon beyond 3 min), 1 = retention from 3–5 min, 2 = retention beyond 5 min. Aerosol "hot spot" abnormalities were classified as either hilar, hilar plus peripheral deposition, or peripheral only. The intensity of this aerosol activity also was scored: 0 = no hot spots present, 1 = mild to moderate intensity of the hot spot, and 2 = markedly intense hot spot activity.

Data Analysis

At each of the two participating institutions, one observer interpreted the gas, aerosol, and perfusion study independently of the others and according to the above-described scoring system. Since the washout phase of xenon ventilation study has been shown to be more sensitive than single breath phase (*5*), xenon ventilation study was analyzed as abnormal if any of the regions had abnormalities either on single breath, washout, or both. Subsequently, the gas ventilation pattern peripheral to the areas of aerosol hot spots was simultaneously examined by placing gas and aerosol images side by side. A separate analysis also was made of the overall correspondence between gas and aerosol

studies (i.e., the proportion with identical scores on both tests). In the discordant zones observed on xenon/aerosol and krypton/aerosol (i.e., zones normal by one, abnormal [score 1 or 2] by the other) the presence of ventilation/perfusion match or mismatch was recorded to determine the effect on PE probability determination. In this regard, the criteria of Biello (*14*) were employed to evaluate the likelihood of PE in the discordant region of interest.

RESULTS

A total of 180 zones were analyzed with respect to xenon and aerosol findings (Table 1). Complete agreement was found in 115 zones (64%). Of these, 76 zones were normal and 39 zones were concordant abnormals (identical scores). Concordant abnormal zones revealed decreased parenchymal aerosol activity corresponding to areas of decreased ventilation on a single breath ^{133}Xe view or retention seen on the ^{133}Xe washout phase (Fig. 1). Discordant results were found between aerosol and ^{133}Xe studies in 65 zones: 51 showed ^{133}Xe abnormalities but a normal radioaerosol distribution. Grade-2 abnormalities were seen in 21 of these zones and 30 had mild to moderate ^{133}Xe abnormalities (Score 1). Of these 51 zones, 47 had ^{133}Xe washout abnormalities only. In five other discordant zones, the ^{133}Xe study was graded as normal and the aerosol as abnormal. In the final nine discordant zones, both the ^{133}Xe and aerosol findings were abnormal but the degree of abnormality was scored differently (Table 1).

A total of 144 zones were analyzed on krypton and aerosol studies (Table 2). Of these, 123 (85%) were in complete agreement, 94 being concordant normals and 29 having identical abnormal scores. In two zones, the ^{81m}Kr images were scored as abnormal and the aerosol images as normal, but in 12 zones the ^{81m}Kr study was normal and the aerosol abnormal (Score 1, Fig. 2). Seven other zones demonstrated abnormalities by both methods, graded as more abnormal on the ^{81m}Kr images.

In order to assess the impact of discordant xenon/

TABLE 1
Combined Six-Zone Regional Comparison Results Between Xenon (S.B. and/or W.O.* and Aerosol

[^{99m}Tc]DTPA aerosol	Xenon 0†	1	2
0	76	30	21
1	4	22	5
2	1	4	17

*S.B. = Single breath; W.O. = washout.
† 0 = Normal, 1 = ↓ ≤50% of a region, and 2 = ↓ in >50% of a region.

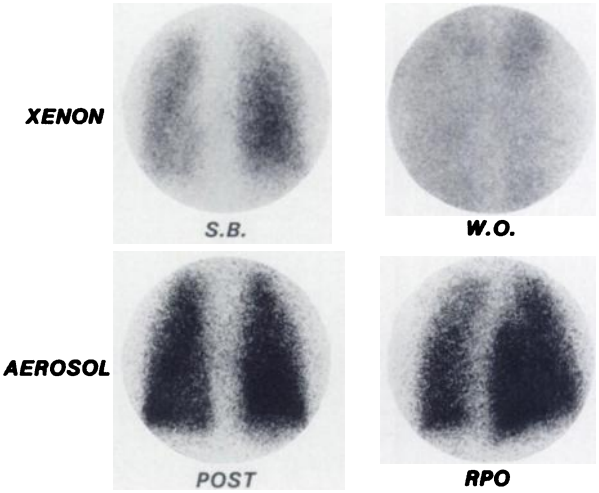


FIGURE 1
Decreased xenon ventilation in right upper lung on single breath (S. B.) with focal area of retention in washout (W.O.) phase. Aerosol images show decreased parenchymal aerosol deposition in right upper lung. This 72-yr-old man had normal chest radiograph and was evaluated for chest pain

TABLE 2
Combined Six-Zone Regional Comparison Results Between Krypton and Aerosol

[^{99m}Tc]DTPA aerosol	Krypton-81m 0*	1	2
0	94	2	0
1	12	24	2
2	0	5	5

*0 = Normal, 1 = ↓ ≤50% of a region, 2 = ↓ in >50% of a region.

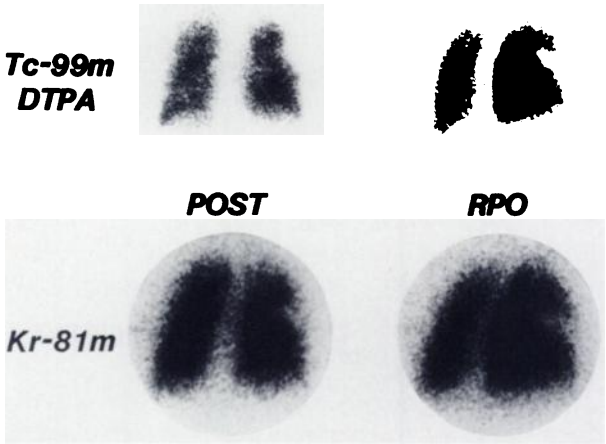
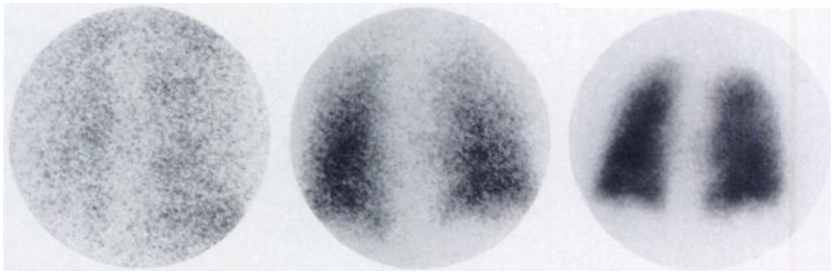


FIGURE 2
Example of aerosol abnormalities appearing more abnormal than ^{81m}Kr. This 70-yr-old woman presented with right pleuritic chest pain with scarring in right lower lung on chest radiograph

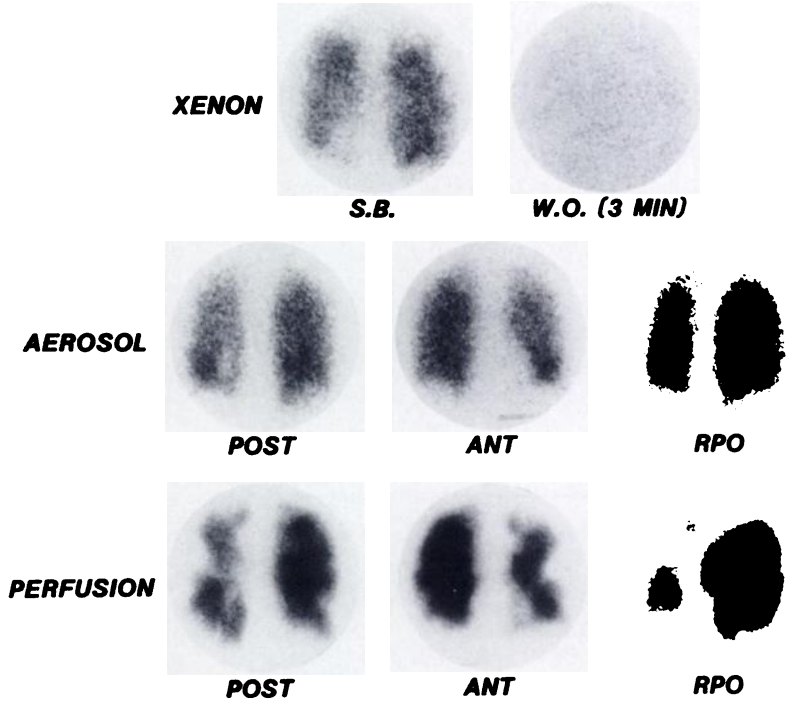
FIGURE 3
Minimal patchiness in distribution of perfusion is seen with areas of retention in ^{133}Xe washout (W.O.) phase and relatively normal aerosol distribution. This was common finding in regions with ^{133}Xe/aerosol discordance. Despite discordance, scintigraphic estimates of PE probability (i.e., low) were not changed in this patient. This 70-yr-old man had history of smoking and was being evaluated for chest pain. His chest radiograph was normal



aerosol and krypton/aerosol findings on the scintigraphic probability of PE, perfusion was examined in the discordant zones. In 44 of the 65 discordant zones (68%) seen in the ^{133}Xe/aerosol pair, perfusion abnormalities were not large enough to cause serious consideration of PE (Fig. 3). In 13 of the zones, perfusion was normal and in 31 perfusion was patchy (<25 of a segment). In all these, there were only washout abnormalities on xenon study. In seven other zones, where the perfusion abnormality was discrete or segmental, the perfusion score was much greater than either the ventilation or aerosol score and both suggested a relative ventilation/perfusion mismatch (Fig. 4). Of these, four had minor xenon abnormalities on the single breath study only. In the remaining three, isolated washout abnormalities were noted. In the five zones where ^{133}Xe activity was normal and the aerosol appeared abnormal, the aerosol defect was in some other projection than the standard posterior view acquired with the ^{133}Xe study. These regions, however, demonstrated normal perfusion and the final outcome of scintigraphic PE probability was not changed. In the nine zones where both xenon and aerosol findings were abnormal, but to a different degree, there were associated perfusion abnormalities more similar to the aerosol defects than the xenon findings. Nevertheless, all would have been interpreted as matched abnormalities by both methods.

Analysis of ^{81m}Kr and aerosol zones revealed 21 discordant zones. In 12, aerosol was scored as mildly abnormal (Score 1) and ^{81m}Kr as normal. In two zones, aerosol was normal and ^{81m}Kr was mildly abnormal, and in seven both were abnormal, but to a different degree. In two, the ^{81m}Kr defects were greater than those seen in the aerosol study and in five the reverse was true. All 21 discordant zones showed normal or minimally abnormal patchy perfusion defects. Therefore, the final probability of PE based on the scintigraphic criteria was the same with aerosol perfusion and ^{81m}Kr perfusion studies in all the patients with discordant zones.

FIGURE 4
Xenon study showing mild nonhomogeneity during single breath (S.B.) phase associated with normal aerosol study. Discrete and segmental perfusion abnormalities are seen. Despite discordance between single breath xenon and aerosol, relative ventilation-perfusion mismatch was maintained on both xenon/perfusion and aerosol/perfusion studies, and both resulted in high probability for PE interpretation. This illustration also emphasizes that no significant carry-over activity from aerosol study is noted on perfusion image



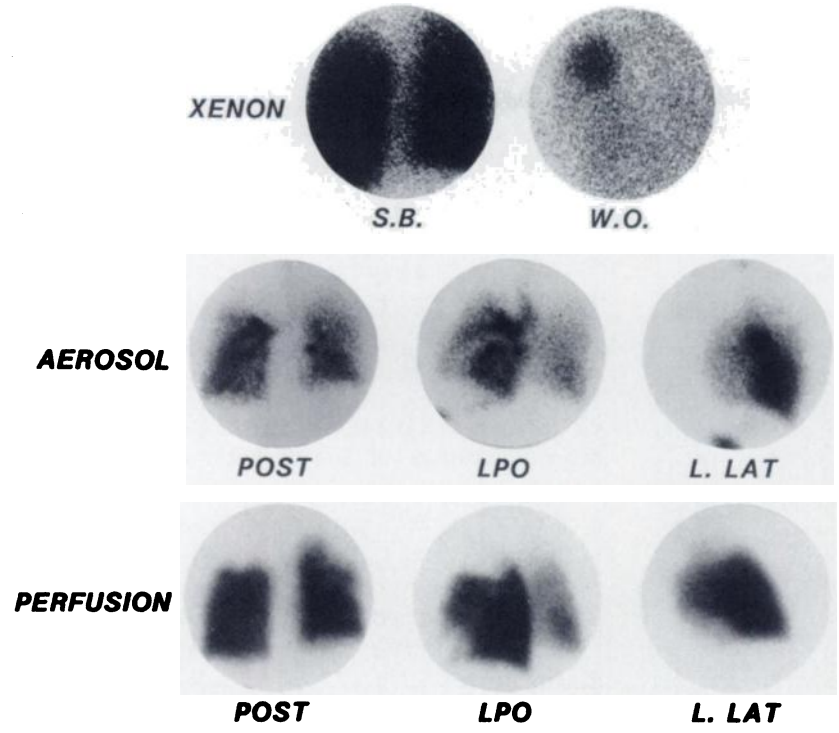


FIGURE 5
Aerosol study where both central and peripheral "hot spots" are associated with reduced parenchymal aerosol deposition, definite focal area of ^{133}Xe retention, and matching perfusion abnormality in left upper lung zone. Scintigraphic probability of PE is indeterminate on both ^{133}Xe and aerosol studies. This 54-yr-old woman was evaluated for chest pain and shortness of breath; chest radiograph demonstrated only left upper lung nodule

Aerosol Turbulence or Hot Spots

Aerosol hot spots were seen in 25 zones in nine patients who had ^{133}Xe and aerosol studies; hilar deposition was seen in 10, hilar and more peripheral foci in nine, and peripheral foci alone in six. Abnormal ^{133}Xe washout was seen in 19 zones (76%) peripheral to hot spots (Fig. 5). Peripheral aerosol activity patterns were abnormal in only 11 of these zones (44%). Hot spots were seen in 20 zones in eight patients with krypton/aerosol studies; hilar deposition was seen in six, hilar plus peripheral foci in four, and peripheral foci alone in ten. Krypton ventilation was abnormal in nine regions (45%) peripheral to the hot spots and each of these regions had an abnormal peripheral aerosol deposition pattern. There was no correlation between the intensity or size of the hot spots and the ventilation findings peripheral to the hot spots.

DISCUSSION

Radioaerosols differ from ^{133}Xe and ^{81m}Kr in that they are particulates rather than gases. The washout component of ^{133}Xe ventilation studies has been shown to be extremely sensitive in detecting chronic obstructive pulmonary disease (*4,5*). Neither aerosol nor krypton studies have a washout component, which may reduce their sensitivity in detecting airway disease. Does the lack of a washout phase in aerosol studies cause the false appearance of ventilation/perfusion mismatches in the presence of obstructive airways disease? The comparability of PE probability estimates obtained from independent readings of aerosol and ventilation studies combined with perfusion images (*12*) infers that this is not a problem. The actual regional data needed to answer the question, however, were not described in that previous study. Similarly, previous findings (*15–17*) of associations between aerosol hot spot abnormalities and airways disease have not been extended to regional analysis after use of the newer aerosol systems.

The current study demonstrates 64% concordance between xenon and aerosol studies on a regional basis and an 85% concordance between krypton and aerosol studies. The closer agreement between ^{81m}Kr and aerosol studies probably is based on similarities in image presentation, i.e., ^{81m}Kr studies are obtained in many views and do not have a washout phase. The results also verify again that the washout phase of ^{133}Xe studies is the most sensitive scintigraphic monitor of airways disease. The fact that aerosol studies were minimally abnormal in 12 zones where ^{81m}Kr images were interpreted as normal is probably related to technique. The same low-energy collimator was used to image both the 140 KeV photon of [^{99m}Tc]DTPA and 190 KeV ^{81m}Kr activity. The resolution of defects at 190 KeV is somewhat lower, and subtle ^{81m}Kr defects may have been missed.

The discrepancies between aerosol and gas ventilation findings did not impact on final scintigraphic probability of pulmonary embolism in this series. This was mainly because the majority of zones associated with abormal ^{133}Xe washout alone had normal or only min-

imal abnormal perfusion. This confirms other observations (5) that ^{133}Xe studies are even more sensitive to airways disease than the perfusion scan. The results also suggest that when airways disease is severe enough to cause a significant perfusion abnormality, it also usually is severe enough to cause parenchymal aerosol abnormalities.

The current study further confirms regionally that the presence of central aerosol hot spots usually does not cause a significant problem for assessing peripheral ventilation/perfusion mismatch or matches. Perhaps this is because the improved aerosol generator systems produce submicronic particles that penetrate effectively beyond areas of central airways turbulence. The majority (76%) of xenon zones distal to the hot spots noted on the aerosol study had mild washout abnormalities, while approximately 50% of the zones presented with either a normal parenchymal aerosol pattern or a normal ^{81m}Kr appearance. This suggests that the central airways abnormalities that cause focal aerosol deposition frequently are not accompanied by significant distal airways disease or morphologic abormalities. It also suggests that ^{133}Xe and ^{81m}Kr are relatively insensitive to central abnormalities that cause turbulent air flow in large airways. This does not necessarily contradict the idea that most airways diseases first affect peripheral, small airways rather than major bronchi, but does suggest that some causes of central aerosol deposition are more functional than anatomic. For instance, short-term increase in the amount of mucous moved centrally by mucociliary clearance could cause transient increases in central airway turbulence and lead to aerosol hyperdeposition. This "independence" of central and peripheral findings is also supported by the lack of a relationship between the intensity of overall amount of central deposition and the degree of peripheral parenchymal ventilation abnormalities.

In conclusion, the regional diagnostic information on aerosol studies seems equivalent to that provided by ^{133}Xe and ^{81m}Kr imaging with respect to the scintigraphic diagnosis of pulmonary embolism. The xenon washout phase detects more peripheral pulmonary abnormalities than either aerosol or ^{81m}Kr studies, but is not any more effective for evaluating ventilation-perfusion concordance in areas with significant perfusion defects. Discordant xenon/aerosol and krypton/aerosol zones did not impact adversely on estimates of the scintigraphic probability of pulmonary embolism when compared to gas perfusion studies. Aerosol studies with [^{99m}Tc]DTPA thus seem well suited for the scintigraphic evaluation of regional ventilation and ventilation-perfusion concordance.

REFERENCES

1. Kelly MJ and Elliot JP: The radiological evaluations of patients with suspected pulmonary thromboembolic disease. *Med Clin North Am* 52:3, 1974
2. Poulose KP, Reba RC, Gildoy DL, et al: Diagnosis of pulmonary embolism: A correlative study of the clinical, scan and angiographic findings. *Br Med J* 3:67, 1970
3. McNeil BJ, Holman BL, Adelstein J: The scintigraphic diagnosis of pulmonary embolism. *JAMA* 227:743, 1974
4. Alderson PO, Secker-Walker BH, Forrest JV: Detection of obstructive pulmonary disease: Relative sensitivity of ventilation-perfusion studies and chest radiography. *Radiology* 112:643–648, 1974
5. Alderson PO, Lee H, Summer WR, et al: Comparison of Xe-133 washout and single-breath imaging for detection of ventilation abnormalities. *J Nucl Med* 20:917–922, 1979
6. Fazio F: Assessment of regional lung ventilation by continuous inhalation of radioactive krypton-81m. *Br Med J* 3:673, 1975
7. Goris ML, Daspit SG, Walter JR, et al: Application of ventilation lung imaging with ^{81m}krypton. *Radiology* 122:399–403, 1977
8. Taplin GV, Chopra SK: Inhalation lung imaging with radioactive aerosol and gases. In *Progress in Nuclear Medicine*, Vol. 5, Guter M, ed. Basel, S. Karger, 1978, pp 119–143
9. Pircher FJ, Temple JR, Kirsch WT, et al: Distribution of pulmonary ventilation determined by radioisotope scanning. *AJR* 94:807–814, 1965
10. Taplin GV, Poe ND, Greenberg A: Lung scanning following radioaerosol inhalation. *J Nucl Med* 77:87, 1966
11. Taplin GV: Scintiscanning in the assessment of regional pulmonary function: Clinical cardiopulmonary physiology. In *Cardiopulmonary Physiology*, Gordon BL, ed. New York, Grune & Stratton, Inc., 1969, pp 437–646
12. Taplin GV, Poe ND: A dual lung scanning technique for evaluation of pulmonary function. *Radiology* 85:365–368, 1965
13. Alderson PO, Biello DR, Gottschalk A: Tc-99m DTPA aerosol and radioactive gases compared as adjuncts to perfusion scintigraphy in patients with suspected pulmonary embolism. *Radiology* 153:515–521, 1984
14. Biello DR, Mattar AG, McKnight RC, et al: Ventilation perfusion studies in suspected pulmonary embolism. *AJR* 133:1033–1037, 1979
15. Ramanna L, Tashkin DP, Taplin GV, et al: Radioaerosol lung imaging in chronic obstructive pulmonary disease: Comparison with pulmonary function tests and roentgenography. *Chest* 68:634–640, 1975
16. Taplin GV, Chopra SK: Lung perfusion-inhalation scintigraphy in obstructive airway disease and pulmonary embolism. *Radiol Clin North Am* 16:491–513, 1978
17. Isawa T, Wasserman K, Taplan GV: Lung scintigraphy and pulmonary function studies in obstructive airway disease. *Am Rev Resp Dis* 102:161, 1970