^{99m}Tc Technegas Ventilation and Perfusion Lung Scintigraphy for the Diagnosis of Pulmonary Embolus

Douglas M. Howarth, Linda Lan, Paul A. Thomas and Leonard W. Allen

Department of Nuclear Medicine, John Hunter Hospital, Newcastle, New South Wales, Australia

Lung scintigraphy is used widely for diagnosis of pulmonary embolus (PE). Technegas ventilation imaging has many advantages over other methods, but little outcome data exists on this technique. The aims of this study were to better define the role of lung scintigraphy in the management of patients with suspected PE and to evaluate technegas ventilation imaging by following patient outcomes. **Methods:** A group of 717 out of 834 consecutive patients, referred to a university teaching hospital for lung scintigraphy to confirm or refute the diagnosis of PE, was followed for 18–30 mo to determine clinical outcome. The follow-up endpoints were death as a result of PE, death as a result of hemorrhage after treatment for PE, uncomplicated survival, survival with subsequent PE, nonfatal hemorrhage after treatment for PE and recurrence of PE in treated patients. Ventilation imaging was performed using technegas, and perfusion imaging was performed using intravenous ^{99m}Tc macroaggregated albumin. The modified PIOPED (Prospective Investigation of Pulmonary Embolism Diagnosis) diagnostic criterion was used for interpretation of lung scintigraphy. **Results:** Diagnostic results included 3.5% normal studies, 67.4% assessed as low probability for PE, 10% as moderate probability for PE and 19.1% as high probability for PE. A total of 231 patients received therapy with heparin, followed by warfarin, including those receiving anticoagulation therapy for other conditions. Ninety-six percent of patients with normal and low probability studies (n = 508) had good outcomes, 6 patients died as a result of PE and 12 subsequently developed PE. The odds ratio for death by PE in this group was 0.2. Of the 72 moderate probability studies, 39 patients were untreated. In this group there was 1 death due to PE, and PE subsequently developed in 2 patients. None of the remaining 33 treated patients died, but 4 patients experienced bleeding complications. The odds ratio for death by PE in the moderate probability group was 0.7. In those patients with high-probability studies, there were 8 deaths by PE, 6 deaths by hemorrhage, 11 nonfatal hemorrhages and 7 patients who experienced recurrences of PE. The odds ratios in this group were 6 and 10 for death by PE, or death by PE and the treatment of PE, respectively. **Conclusion:** The use of the modified PIOPED diagnostic classification is valid for technegas lung scintigraphy. Using technegas, normal/low-probability and high-probability results are highly predictive of respective outcomes. Technegas lung scintigraphy reduces the number of indeterminate studies.

Key Words: pulmonary embolus; lung scintigraphy; technegas

J Nucl Med 1999; 40:579–584

The diagnosis of life-threatening pulmonary embolus (PE) remains an imperfect process using any of the techniques currently available. A paucity of outcome data prevents direct comparison of techniques, and even the de facto "gold standard" of pulmonary angiography offers limited outcome data to validate its status. Ventilation and perfusion lung scintigraphy is a noninvasive and widely used test for the diagnosis of PE. Although the technique for perfusion lung scintigraphy is standardized, the techniques available for ventilation imaging vary considerably. Ventilation scintigraphy techniques commonly used in the U.S. include the administration of ^{133}Xe gas, ^{81m}Kr gas and aerosolized ^{99m}Tc-diethylenetriamine pentaacetic acid. Technegas ventilation imaging, using inhaled metallofullerenes to deliver radiotracer to the alveoli, has been used widely in Australia since 1986 and more recently in southeast Asia and Europe. This technique has been proven safe and effective and has the advantage of allowing a complete series of ventilation images of the lung (for example, six projections) to be matched to the same perfusion images (*1–5*). This facilitates the detection of mismatched distribution of radiotracer on ventilation and perfusion imaging. A widely adopted diagnostic criterion for the detection of PE by lung scintigraphy is the modified Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) classification (*6,7*). This, however, was devised for use with ^{133}Xe gas ventilation imaging and has not been validated by a large-scale outcome study using other ventilation techniques.

The aims of this study were to better define the role of lung scintigraphy in the management of patients with suspected PE and to evaluate technegas ventilation imaging by following patient outcome.

MATERIALS AND METHODS

A total of 834 patients were investigated by lung scintigraphy between July 1994 and June 1995 at the John Hunter Hospital, Newcastle, New South Wales (NSW), Australia. This institution is a tertiary referral university teaching hospital, serving a population of more than a million. Patients were referred consecutively by a wide range of general practitioners and specialists for diagnosis of

Received Mar. 4, 1998; revision accepted Sep. 15, 1998.

For correspondence or reprints contact: Douglas M. Howarth, MD, Department of Nuclear Medicine, John Hunter Hospital, Locked Bag No. 1, Newcastle Regional Mail Centre 2310, New South Wales, Australia.

suspected PE after full clinical evaluation. Institution approval was obtained for data collection. Approval was also obtained from referring physicians and the NSW Department of Births, Deaths and Marriages. Median patient age was 67 y, with an age range of 16–96 y. Fifty-seven percent of patients were female and 43% were male. All patients were followed up, and outcome was assessed in December 1996 by contact with the patient or the patient's physician, review of hospital or clinical case records and, when appropriate, postmortem data and death certificate information obtained through the Department of Births, Deaths and Marriages. All investigations for pulmonary embolus or deep-vein thrombosis and hospital admissions were noted during the follow-up period. During the follow-up period, a patient was considered to show no PE only if he or she was (a) not hospitalized with suspected thromboembolism, (b) not worked up for subsequent PE and (c) did not die. The study outcome endpoints were: death as a result of PE, survival with subsequent PE, uncomplicated survival, recurrence of PE after treatment, death as a result of hemorrhage after treatment of PE and nonfatal hemorrhage after treatment of PE. The decision to initiate anticoagulation therapy in each patient was made by the referring physician on the basis of the lung scintigraphy result, clinical assessment and, in the case of 7 patients, the results of pulmonary angiography. Pulmonary angiography was not performed more widely because of funding constraints and nonuniform expertise among the radiologists interpreting these studies. The standard anticoagulation therapy consisted of intravenous heparin monitored by activated partial thromboplastin time daily, followed by oral warfarin therapy, monitored by the international normalized ratio. Oral anticoagulation therapy was continued for a minimum of 3 mo. A false-negative lung scintigraphy study was defined by high clinical suspicion or repeat lung scintigraphy within 28 d of the original study showing change from normal, low or moderate probability for PE to high probability, or change from normal or low probability for PE to moderate probability. Recurrent PE was defined by a pattern of new or significantly altered perfusion defects seen on a repeat study performed within the follow-up period.

The generation of technegas (Tetley Manufacturing, Sydney, Australia) required 370–740 MBq ^{99m}Tc-sodium pertechnetate in a volume of 0.1 mL to be instilled into a small carbon crucible placed between electrodes and heated to 2500°C for 15 s in the presence of argon gas. The radiolabeled metallofullerenes gas mixture was then administered to the patients through closed, single-use circuit breathing tubes until a counting rate of 2000 counts/s was attained.

Ventilation imaging was performed with inhaled technegas, and six standard views (anterior, posterior, left and right anterior oblique and left and right posterior oblique) were obtained with up to 200,000 counts per view acquired in 256 × 256 matrix size. The same six views were obtained for perfusion imaging after 170–190 MBq ^{99m}Tc macroaggregated albumin were intravenously administered. All perfusion images had more than 500,000 counts per view, acquired in 256 × 256 matrix size. The ventilation-to-perfusion count ratio was always greater than 4. This ratio was never reduced as a result of deposition of particles in the central airways. Imaging was performed using Elscint-SP4 and SP6WB gamma cameras, each with a dedicated computer (Elscint, Haifa, Israel). Low-energy, medium-resolution collimation was used for all image acquisitions.

Interpretation of lung scintigraphy was undertaken by four experienced nuclear medicine physicians, who were blinded to detailed clinical information. When matched ventilation and perfusion defects were seen on lung scintigraphy, a recent chest radiograph was used to aid interpretation. The modified PIOPED diagnostic criterion was used for all lung scintigraphy reports (*8*). Interobserver reporting reproducibility was performed using two teams, each unaware of the other's reports. When two reporting physicians could not agree, a third physician provided majority agreement without clinical information resulting in bias. Intraobserver reporting reproducibility was performed 3 mo after the initial lung scintigraphy interpretation, by repeat random-sequence reporting by one physician. All reporting was performed using a computer with a 250-gray-scale register.

Comparative statistical analysis was performed using the relative deviate test (*9*). Odds ratios and diagnostic reproducibility were calculated according to previously reported methods (*10–13*).

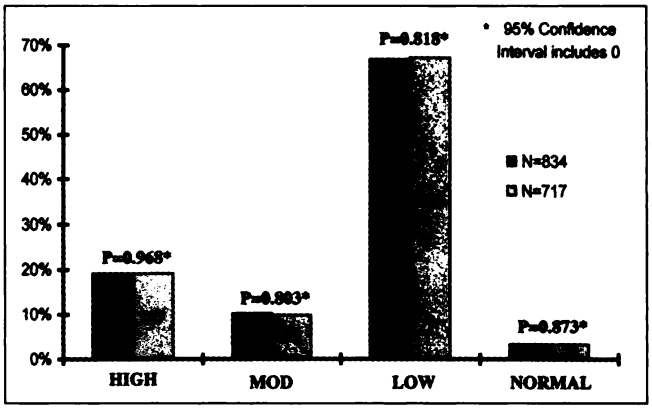

FIGURE 1. Comparison of lung scintigraphy results for total number of patients enrolled (n = 834) and total patients with documented outcome data (n = 717). All *P* values and 95% confidence intervals calculated by relative deviate test.

RESULTS

Of the 834 patients, 117 were lost during follow-up as the result of unknown addresses, refusal to consent to follow-up or inadequate case notes. For each diagnostic category, no significant difference was found ($P > 0.8$, relative deviate test) between the lung scintigraphy results of the total patients studied (n = 834) and the total cohort (n = 717), indicating that the outcome data were obtained on a representative patient sample (Fig. 1). Of the 717 patients, 231 received anticoagulation therapy (Table 1). There were 183

TABLE 1
Lung Scintigraphy Results as Probabilities for Pulmonary Embolus

	Normal (%)	Low (%)	Moderate (%)	High (%)
Overall (n = 717)	25 (3.5)	483 (67.4)	72 (10)	137 (19.1)
Therapy (n = 231)*	2 (8)	90 (19)	33 (46)	106 (77)

*Including anticoagulation therapy for reasons other than pulmonary embolus.

Results classified as normal, low, moderate or high probability for pulmonary embolus on lung scintigraphy.

TABLE 2
Cause of Death in Patients Investigated for Pulmonary Embolus by Lung Scintigraphy

Cause of death (n=183)	No. of patients
Pulmonary embolus	15
Hemorrhage (due to anticoagulation)	6
Cancer	31
Sepsis	22
Myocardial infarction	28
End-stage cardiac failure	31
End-stage respiratory failure	33
Acute/chronic renal failure	8
Cerebrovascular accident	3
Ruptured abdominal aortic aneurysm	5
Bowel infarction	1

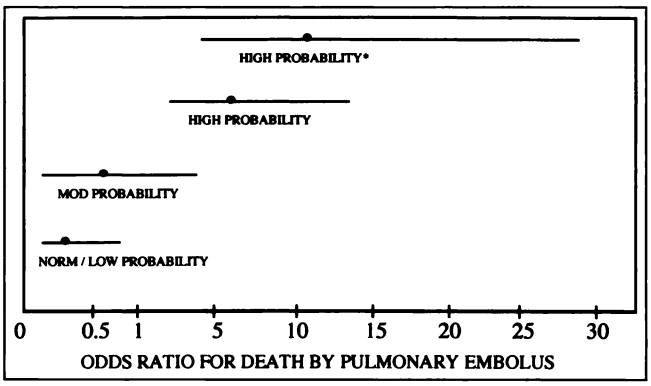

FIGURE 2. Comparative odds ratios for death by PE in patients classified as normal (norm)/low, moderate (mod) or high probability for PE by lung scintigraphy. 95% confidence intervals are shown. Asterisk indicates odds ratio for death by PE or treatment with anticoagulation therapy.

deaths among the 717 patients who were followed up. Included among the deaths were 15 patients who died of PE and 6 patients treated for PE who died of hemorrhage. The remaining causes of deaths were representative of patients in a tertiary referral hospital (Table 2).

Diagnostic reproducibility assessed by intraobserver agreement was 97% (κ = 93%) and between 82% and 99% (κ = 83%) for each diagnostic classification (Table 3). Interobserver agreement was highest for normal (99%) and low probability results (96%), and lowest for moderate probability (84%) and high probability (82%).

Normal and Low-Probability Studies

Because of the complete ventilation data provided by technegas, lung scintigraphy reporting varied slightly from the modified PIOPED classification, in that a study was considered to be normal only when both perfusion and ventilation were normal. This interpretation of lung scintigraphy prevented a potentially confusing report, with normal perfusion but abnormal ventilation. Consequently, only 25 patients in this study were classified as normal, and 483 were classified as low probability for PE. Ninety-two of these patients received anticoagulation therapy for reasons other than PE, including chronic arrhythmia (5.4%), valvular heart disease (8.7%), left ventricular thrombus (13%), peripheral vascular disease (6.5%), cerebrovascular disease (3.3%), recent prolonged immobilization or surgery (37%) or previous venous thrombosis (26.1%). Apart from some patients with valvular heart disease, anticoagulation therapy was generally kept within the lower therapeutic range for these patients.

TABLE 3
Diagnostic Reproducibility of Lung Scintigraphy Reporting

Interobserver agreement	
Normal study	99%
Low probability	96%
Moderate probability	84%
High probability	82%
Kappa	83%
Intraobserver agreement	97%
Kappa	93%

Results are shown for normal, low, moderate and high probability for pulmonary embolus.

Most of the 508 patients with normal and low-probability diagnoses experienced uncomplicated survival (490 or 96%). Six patients died of PE, and in 12 patients PE developed within 28 d of the original lung scintigraphy. Pulmonary angiography was performed within 48 h of lung scintigraphy in 4 patients who were classified as low probability for PE. In 1 patient, angiography showed pulmonary vein thrombus (false-negative lung scintigraphy), and the remaining 3 patients had negative angiography results. The odds ratio for death by PE in patients with a normal or low-probability study was 0.2 (Fig. 2).

Moderate-Probability Studies

Seventy-two patients (10%) were classified in the moderate probability for PE group. The decision to initiate anticoagulation therapy was based on the pretest probability of PE, and on this basis 33 patients were treated. In this treated group, there were no deaths by PE, but 4 patients had serious bleeding complications related to treatment. Of the remaining 39 untreated patients, 1 died as a result of PE, and 2 patients were subsequently found to have PE on repeat imaging. The odds ratio for death by PE, for those classified as moderate probability, was 0.7 (Fig. 2). Two patients underwent pulmonary angiographies that were negative for PE.

High-Probability Studies

Of the 717 patients, 137 (19.1%) were classified as high probability for PE. Of these patients 106 (77%) received long-term anticoagulation therapy. One patient underwent angiography, which was negative (false-positive lung scintigraphy), and therefore received no anticoagulation medication. There were 8 deaths as a result of PE. These patients died before therapeutic anticoagulation was achieved. The remaining 22 patients were considered unsuitable for long-

TABLE 4
Serious but Nonfatal Complications of Anticoagulation Therapy in Patients Treated for Pulmonary Embolus

Gastrointestinal	7
Severe hematoma	3
HITTS	2
Pericardial hemorrhage	1
Wound hemorrhage	1
Severe hemoptysis	1
Total	15

HITTS = heparin-induced thrombocytopenia thrombosis syndrome.

TABLE 5
Lung Scintigraphy Results of Patients with Subsequent Poor Outcomes

	Normal	Low	Moderate	High
Death by PE (n=15)	0	6	1	8
Death by hemorrhage (n=6)	—	—	—	6
Subsequent PE (n=14)	0	12	2	0
Recurrent PE (n=7)	—	—	—	7
Hemorrhage (n=15)	—	—	4	11

PE = pulmonary embolus.

term anticoagulation therapy and were treated with inferior vena cava filters, subcutaneous calcium heparin or aspirin therapy. Six patients who received long-term anticoagulation therapy died of hemorrhage, and an additional 11 patients experienced serious nonfatal hemorrhages (Table 4). Seven patients had recurrences of PE, including 4 who did not receive long-term anticoagulation therapy. The odds ratio for deaths by PE was 6, and the odds ratio for death by PE or its treatment was 10 (Fig. 2).

Comparative Outcome

All patients with normal lung scintigraphy survived without complications. Complication-free survival was also noted in 96% of patients classified as low probability for PE, 94% of patients classified as moderate probability for PE and 77% of patients classified as high probability for PE (Fig. 3). Clinically significant PE was missed in 2.9% of patients who underwent lung scintigraphy and were initially classified as low or moderate probability for PE. These included 7 patients who died as a result of PE and 14 patients who developed PE after scintigraphy (Table 5). Of those patients who received anticoagulation therapy, 21 had serious bleeding complications (9%). Comparison of patients on anticoagulation medication with untreated patients showed that for patients with a high-probability classification, significantly more patients on anticoagulation medication had complication-free survival compared with untreated patients ($P < 0.003$). Conversely, for patients with lung scintigraphy classified as normal or low probability, significantly more untreated patients had complication-free survival compared with patients on anticoagulation medication ($P < 0.003$ and $P = 0.004$, respectively) (Fig. 3, Table 6). For patients classified as moderate probability for PE, no significant difference of outcome was found between untreated patients and patients on anticoagulation medication ($P = 0.575$).

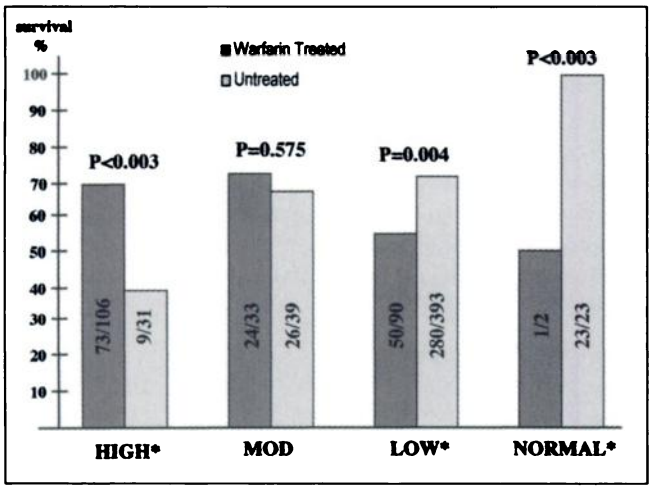

FIGURE 3. Comparison of complication-free survival (n = 486) among patients untreated and patients treated with warfarin. Patients are classified as normal, or as low, moderate (mod) or high probability for PE by lung scintigraphy. All *P* values calculated by relative deviate test.

DISCUSSION

Interpretation of ventilation/perfusion lung scintigraphy for the diagnosis of PE has been described as confusing and as having the propensity to result in incorrect clinical decisions (*14*). The use of ^{133}Xe for ventilation imaging, which may not always readily permit direct comparison of

TABLE 6
Patient Outcomes

Outcome	No. of patients	% of total (n=717)
Patients treated for PE (n=139)		
Death by PE	8	5.8%
Recurrent PE	7	5.0%
Death by hemorrhage	6	4.3%
Life-threatening hemorrhage	15	10.8%
Death by other causes	6	4.3%
Complication-free survival	97	69.8%
Patients not treated for PE (n=486)		
Death by PE	7	1.4%
Subsequent PE	14	2.8%
Death by other causes	127	26.2%
Complication-free survival	338	69.6%
Patients anticoagulated for other reason (n=92)		
Death by hemorrhage	3	3.3%
Life-threatening hemorrhage	12	13.0%
Death by other causes	26	28.3%
Complication-free survival	51	55.4%

PE = pulmonary embolus.

all ventilation images with perfusion images, may contribute to this perception. ^{133}Xe washes out of the lung quickly, making multiple views difficult to obtain and, in many instances, impractical. The advantage of technegas over ^{133}Xe for ventilation imaging is that technegas is retained within the alveoli long enough to obtain multiple images, enabling complete image matching to the perfusion study (*15*). When ready comparison can be made between ventilation and perfusion images for all views obtained, true mismatches of ventilation and perfusion can be judged more accurately.

When PE is diagnosed using lung scintigraphy and pulmonary angiography, death is uncommon, provided there is both proper diagnosis and appropriate treatment (*16*). The outcome data presented in this study indicate that lung scintigraphy using technegas ventilation imaging is highly predictive of outcomes in patients classified as at normal, low or high probability for PE. The PIOPED study classified 39% of patients as indeterminate for PE using ^{133}Xe ventilation and perfusion imaging, whereas our data indicated only 10% of patients as indeterminate (classified moderate probability for PE) using technegas ventilation and perfusion imaging (*6*). Review of the PIOPED data showed that by using a definition of PE based on unequivocal angiographic findings or autopsy data, 399 of 1487 patients (27%) had PE confirmed. PE was excluded in 960 patients (64%) who had negative pulmonary angiography and were uneventful at 1-y follow-up. The remaining 128 (9%) were classified as indeterminate (*17*). It is of interest that these results resemble our outcome results of 157 of 717 (22%) for confirmed clinically significant PE, and 560 of 717 (78%) for excluded clinically significant PE. Furthermore, using our lung scintigraphy data, the indeterminate groups are closely matched (9% versus 10%). Similar results have been reported elsewhere. A prospective outcome study of 175 patients investigated by technegas ventilation and perfusion imaging resulted in: 22% high probability for PE, 14% indeterminate and 64% as low probability, very low probability or normal (*18*). A 1-mo outcome study of 100 patients who underwent technegas ventilation and perfusion scintigraphy and were classified as low probability showed that none had clinically significant PE (*19*). The original PIOPED study stated that lung scintigraphy failed to detect 12% of patients with PE and misclassified these as low probability for PE, when pulmonary angiography was used as the "gold standard" for detection of PE. This compares with the 2.9% of our patients misclassified as low probability or moderate probability for PE with poor outcomes, defined as recurrent PE or death by PE. This discrepancy reflects both the difference in diagnostic accuracy of lung scintigraphy techniques used, the different outcome markers and, possibly, different study populations. Another large-scale prospective study, albeit with limited outcome data, demonstrated the value of perfusion imaging (*20*). The authors of that study, however, argued that, with the use of a simplified diagnostic classification, perfusion imaging alone increases diagnostic accuracy for the detection of PE. Incomplete data relevant to clinical outcomes and reliance on pulmonary angiography tend to weaken this argument. The concept of ventilation and perfusion mismatch resulting from PE remains one of the most useful diagnostic clues for the presence of PE (*21*). It is difficult to imagine that when an optimal standard of ventilation imaging is available, perfusion imaging alone would offer any true diagnostic advantage.

Pulmonary angiography or CT methods are yet to be proven as universally optimal outcome markers. Outcome data for 167 untreated patients who had negative pulmonary angiography studies indicate that this test has a good negative predictive value (*22*). The detection of pulmonary emboli by angiographic or CT methods, however, may be of limited use in determining which patients should be treated with long-term anticoagulation therapy. Further refinement of the diagnostic classification of high probability on lung scintigraphy may also be required to ensure a reliable diagnosis of clinically significant PE. Our finding of a 9% bleeding complication rate after anticoagulation is not trivial. Therefore, although it remains important, the detection of PE must be balanced by the correct selection of patients to be treated by anticoagulation therapy. The detection of small or clinically insignificant PE may place the patient on anticoagulation medication at greater risk of bleeding than the benefits of therapy would justify.

Although these results indicate that the modified PIOPED diagnostic classification is appropriate for use with technegas ventilation and perfusion imaging, they do not imply that this is the best diagnostic classification for PE. The interobserver agreement for the high and moderate probability criteria was relatively low compared with the normal and low probability criteria. This indicates that estimation of what represents two or more segments of ventilation/perfusion mismatch may vary from one observer to the next. This may make it difficult to classify a study decisively as high probability or moderate probability for PE. Other authors also have suggested that for technegas ventilation imaging, further modification of the PIOPED classification may be required (*18*).

CONCLUSION

The data from the PIOPED study have provided an important basis for the diagnostic classification of PE, on which further refinement and modification should be made. These data confirm that the modified PIOPED diagnostic classification is appropriate for use with technegas ventilation imaging and standard lung perfusion scintigraphy. In addition, these data indicate that when using technegas ventilation imaging, a normal or low-probability lung scintigraphy result is highly predictive of a good clinical outcome in cases in which the patient is given anticoagulation medication. It is also likely that a high-probability lung scintigraphy result is highly predictive of a good clinical outcome in cases in which the patient receives anticoagula-

tion therapy. However, relatively high morbidity and mortality related to anticoagulation therapy in this group indicates that further refinement of this diagnostic classification may be warranted. Using technegas ventilation for lung scintigraphy reduces the number of indeterminate studies and has the potential to reduce the number of patients requiring pulmonary angiography for the diagnosis of PE.

REFERENCES

1. Burch WM, Sullivan PJ, McLaren CJ. Technegas: a new ventilation agent for lung scanning. *Nucl Med Commun.* 1986;7:865–871.
2. James JM, Herman KJ, Lloyd JJ, et al. Evaluation of Tc-99m technegas ventilation scintigraphy in the diagnosis of pulmonary embolism. *Br J Radiol.* 1991;64:711–719.
3. Lemb M, Oei TH, Eifert H, Günther B. Technegas: a study of particle structure, size and distribution. *Eur J Nucl Med.* 1993;20:576–579.
4. Senden TJ, Moock KH, FitzGerald J, et al. The physical and chemical nature of technegas. *J Nucl Med.* 1997;38:1327–1333.
5. James JM, Testa HJ. The use of Tc-99m technegas in the investigation of patients with pulmonary thromboembolism. *Nucl Med Commun.* 1995;16:802–810.
6. PIOPED Investigators. Value of the ventilation/perfusion scan in acute pulmonary embolism: results of the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED). *JAMA.* 1990;263:2753–2759.
7. Gottschalk A, Sostman HD, Coleman RE, et al. Ventilation-perfusion scintigraphy in the PIOPED study. Part II. Evaluation of the scintigraphic criteria and interpretations. *J Nucl Med.* 1993;34:1119–1126.
8. Freitas JE, Sorosi MG, Nagle CC, Yeomans ME, Freitas AE, Juni JE. Modified PIOPED criteria used in clinical practice. *J Nucl Med.* 1995;36:1573–1578.
9. O'Brien PC, Shampo MA, Robertson JS. Statistics for nuclear medicine. Part 3: A. Comparing two proportions (the relative deviate test and chi-square equivalent). B. Counting data. *J Nucl Med.* 1983;24:269–272.
10. Royal HD. Technology assessment: scientific challenges. *AJR.* 1994;163:503–507.
11. Fleiss JL. Measuring nominal scale agreement among many raters. *Psych Bull.* 1971;76:378–382.
12. Pagano M, Gauvreau K, eds. *Principles of Biostatistics.* Belmont, CA: Duxbury Press; 1993:115–144.
13. McNeil BJ. Ventilation-perfusion studies and the diagnosis of pulmonary embolism: concise communication. *J Nucl Med.* 1980;21:319–323.
14. Goodman LR, Lipchik RJ. Diagnosis of acute pulmonary embolism: time for a new approach. *Radiology.* 1996;199:25–27.
15. Peltier P, De Faucal P, Chetanneau A, Chatal JF. Comparison of technetium-99m aerosol and krypton-81m in ventilation studies for the diagnosis of pulmonary embolism. *Nucl Med Commun.* 1990;11:631–638.
16. Carson JL, Kelley MA, Duff A, et al. The clinical course of pulmonary embolism. *N Engl J Med.* 1992;326:1240–1245.
17. Worsley DF, Alava A. Comprehensive analysis of the results of the PIOPED study. *J Nucl Med.* 1995;36:2380–2387.
18. Bomanji J, Alawadhi H, Beale A, Birkenfeld B, Siraj QH, Britton KE. Clinical outcomes of patients with suspected pulmonary embolism using Tc-99m-technegas as a ventilatory agent for lung scanning. *Nucl Med Commun.* 1992;13:467–477.
19. Bellomo R, Low R, Pianko S, et al. The 1-month outcome of patients with a low probability technegas ventilation/perfusion lung scan. *Nucl Med Commun.* 1994;15:505–510.
20. Miniati M, Pistolesi M, Marini C, et al. Value of perfusion lung scan in the diagnosis of pulmonary embolism: results of the prospective investigative study of acute pulmonary embolism diagnosis (PISA-PED). *Am J Respir Crit Care Med.* 1996;154:1387–1395.
21. McNeil BJ, Holman L, Adelstein J. The scintigraphic definition of pulmonary embolism. *JAMA.* 1974;227:753–756.
22. Novelline RA, Baltarowich OH, Athanasoulis CA, Waltman AC, Greenfield AJ, McKusick KA. The clinical course of patients with suspected pulmonary embolism and a negative pulmonary arteriogram. *Radiology.* 1978;126:561–567.