Low Probability Lung Scan in a Patient at High Risk for Pulmonary Embolism

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CASE HISTORY

A 58-yr-old man was admitted to the hospital for total left knee replacement. His medical history included an episode of deep venous thrombosis (DVT) after left knee surgery 20 yr earlier. The patient was started on warfarin 1 day prior to the current hospitalization and then switched to low molecular weight heparin after surgery. The heparin was stopped on the first postoperative day because blood loss from a drain in the left knee required blood transfusion. He complained of left calf tenderness on the second postoperative day. Plasma D-dimer level was normal (< 250 ng/ml). A Doppler ultrasound study of the legs was ordered. The patient became acutely short of breath and minimally responsive prior to the test. His oxygen saturation on room air was 70%. Oxygen saturation improved to 94% (pO_2, 74 mm) with 100% oxygen delivered by a face mask. An electrocardiogram did not show any acute changes. A chest radiograph showed atelectasis (Fig. 1). The patient received morphine by a patient-controlled analgesia pump. His level of consciousness improved immediately after administration of naloxone. The patient had been hemodynamically stable, except for a brief period of hypotension which quickly responded to a saline infusion of 500 cc. He was taken to the nuclear medicine department for a perfusion-ventilation lung scan which was reported as low probability for pulmonary embolism (PE) (Fig. 2).

Upon return to the intensive care unit, the patient became acutely hypotensive and required several units of blood and one liter of crystalloid. The patient was stabilized and taken to the radiology department for further diagnostic tests. Ultrasound examination did not show any clot in the proximal to mid left thigh, but the study was limited by a knee cast. Two views from a left pulmonary arteriogram demonstrated a large nonocclusive embolus in the left interlobar pulmonary artery (Fig. 3). A bird's nest filter was placed in the inferior vena cava. The patient's physical condition improved, except for continued tenderness in the left calf. Doppler ultrasound of the legs was repeated and was again normal. He was discharged after 10 days without anticoagulation.

The patient returned to the emergency room 1 mo later complaining of left pleuritic chest pain associated with shortness of breath and mild nocturnal cough for the previous 2 days. Arterial blood gas on room air showed a pH of 7.4, pCO_2 33 mmHg, pO_2 85 mmHg, bicarbonate 21.6 mEq/liter, and oxygen saturation
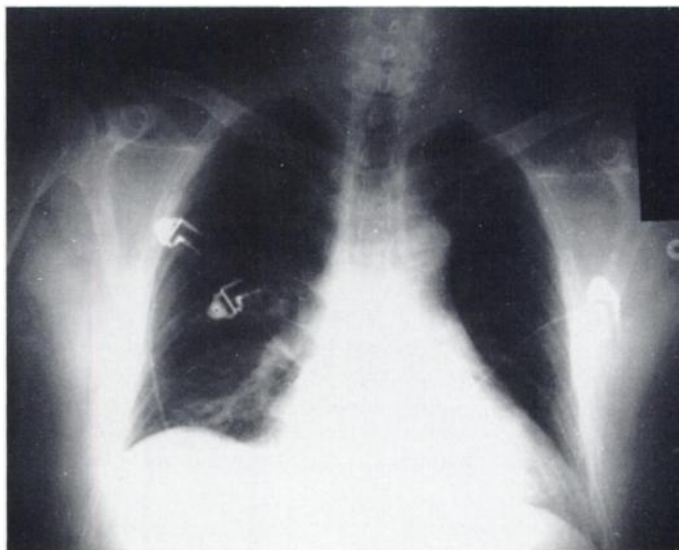
FIGURE 1. Portable chest radiograph obtained at the time of the lung scan demonstrates mild vascular crowding in the left lower lobe due to subsegmental atelectasis. The right lung is clear.

96.5%. The plasma D-dimer level was elevated (1000–2000 ng/ml). Chest radiograph and electrocardiogram were normal. A second lung scan was normal (Fig. 4). The patient was admitted and started on heparin, despite the normal lung scan, because the probability of recurrent PE was high. Helical CT was performed on the following day and did not show any embolus in the medium to large pulmonary vessels nor any thrombus around the bird's nest filter. A second pulmonary arteriogram was normal (Fig. 5). Doppler ultrasound of the legs was also repeated and found to be negative. The anticoagulant was discontinued. The patient's left pleuritic chest pain resolved and he was discharged with a diagnosis of probable chest wall pain.

DISCUSSION

Patients undergoing orthopedic surgery of the legs have a high risk of developing DVT postoperatively. The incidence of DVT is 40%–80%, with fatal PE occurring in 1%–5% (*1*). The incidence of DVT has been reported to be 72% following total knee replacement (*2*). Prophylactic anticoagulant therapy for DVT and PE is routinely employed in orthopedic surgery (*3*). The patient under discussion was started on prophylactic oral anticoagulation 1 day before surgery and low molecular weight heparin after surgery. His care was complicated by severe bleeding into the knee, which required discontinuation of the anticoagulant. The ensuing events represented a very challenging series of diagnostic problems.

Clinical Diagnosis of PE

It is difficult to diagnose PE from history and physical examination since the common presenting symptoms of dys-
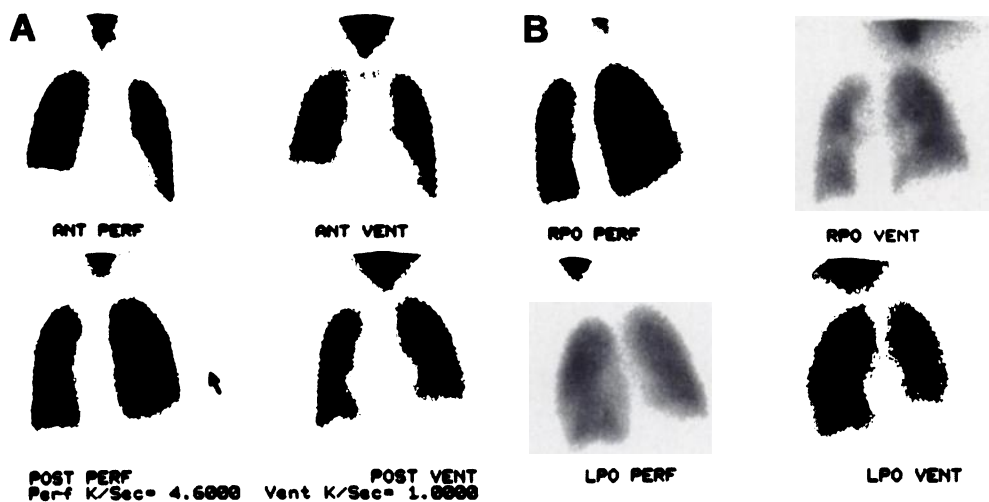
FIGURE 2. (A, B) Ventilation-perfusion lung scan performed with ^{99m}Tc-DTPA aerosol and ^{99m}Tc-MAA shortly before pulmonary arteriography. The studies show matched nonsegmental defects due to the heart and hilar structures. The study indicated a low probability of PE.

pnea, pleuritic chest pain and cough can be caused by other cardiac and pulmonary diseases (4). The classic triad of dyspnea, pleuritic chest pain and hemoptysis is seen infrequently. Signs such as tachypnea, tachycardia and low grade fever are nonspecific. Chest x-ray is rarely diagnostic and is most useful only in excluding other diagnoses. The electrocardiogram can show right-axis deviation and an S-I, Q-III, T-III pattern in patients with right heart strain due to massive PE.
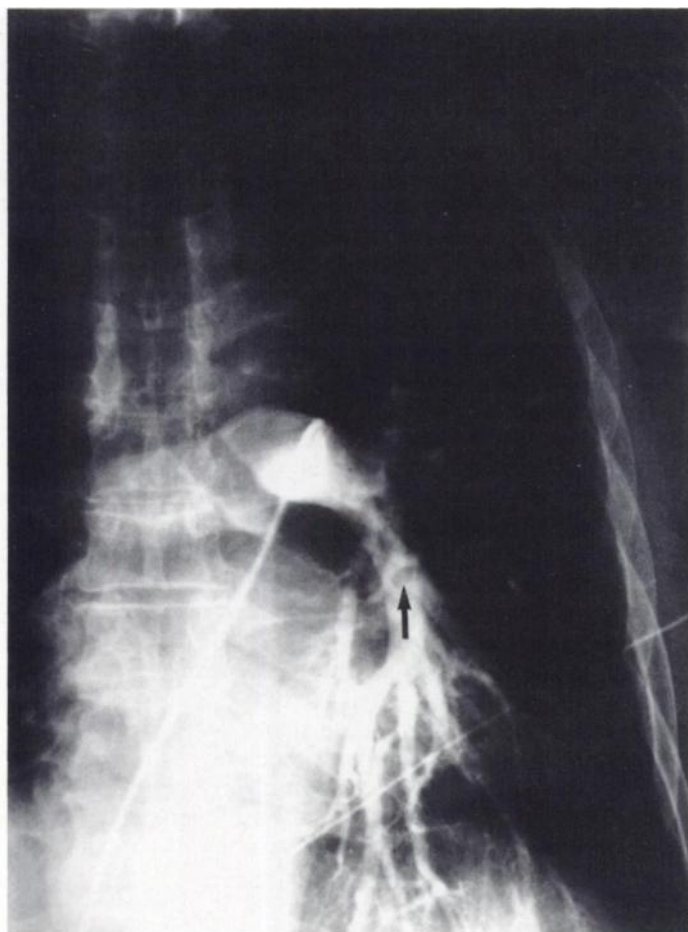

FIGURE 3. Selective pulmonary arteriogram shows a large partially occluded embolus in the left interlobar pulmonary artery (arrow).

This pattern is also nonspecific and seen infrequently. Low arterial blood oxygen saturation supports the suspicion of PE but a normal value does not exclude the diagnosis. Although not diagnostic, symptoms and clinical signs, as well as chest x-ray, electrocardiogram and arterial blood gas may be used to formulate an estimate of the likelihood of PE.

Lung Scintigraphy

The lung scan is an indirect test for PE. Several studies have correlated lung scan patterns with the presence or absence of PE on arteriography (5–9). Different scintigraphic criteria used to estimate the probability of PE are summarized in Table 1.

The PIOPED criteria have been compared to the Biello and McNeil criteria using pulmonary arteriography as the gold standard (10). The likelihood of PE was greater using the PIOPED criteria for high probability than the Biello or McNeil criteria for high probability. The likelihood of a normal arteriogram was greater using the Biello and McNeil criteria for low probability than the PIOPED criteria for low probability. The Biello criteria also resulted in the fewest intermediate probability scans and the lowest number of positive arteriograms in the intermediate category. It was therefore suggested that the Biello criteria represented the best compromise. The original PIOPED data were also reevaluated retrospectively in an effort to improve the accuracy of the criteria.

The study resulted in three modifications of the original criteria (11). The revised PIOPED criteria were also prospectively studied in comparison with the original criteria (12). The revised PIOPED criteria were more accurate, mostly due to increased specificity of the intermediate probability category. The nuclear medicine physicians gestalt impression of the probability of PE, however, was more accurate than either the original or revised criteria. Possible explanations include the recognition of adjunctive signs, such as the stripe sign, and the combination of scan patterns which may be more important than the same findings in isolation.

Significance of a Normal Lung Scan

The PIOPED trial reported that 5/131 patients (3.8%) had PE and a normal or near normal lung scan. The near normal category included scans that were read as very low or low probability by one reader. There were only 21 patients whose studies were interpreted as normal by all readers. None of these patients had PE according to pulmonary arteriography (3 patients) or clinical follow-up (18 patients) (11).
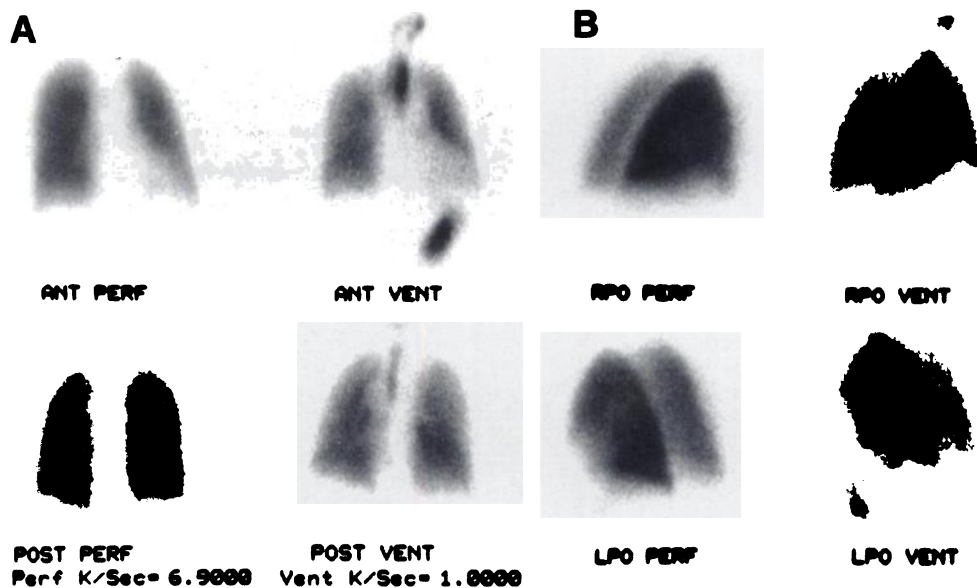
A

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B

FIGURE 4. (A, B) Normal ventilation-perfusion lung scans obtained 33 days after the first study. Perf K/Sec= 6.9000   Vent K/Sec= 1.0000

A normal lung scan essentially rules out clinically significant PE (*13–14*). Sixty-eight patients with normal perfusion lung scans and who were not on anticoagulant therapy were followed for 2–97 mo (*13*). There were no deaths attributable to PE and only one patient had evidence of recent PE 6 mo after the

FIGURE 5. Selective pulmonary arteriogram obtained 2 days after the second lung scan shows resolution of the left interlobar artery embolus demonstrated 1 mo previously.

normal lung scan on autopsy. In a second report, 515 patients with clinical suspicion of PE and a normal perfusion lung scan were followed for 3 mo (*14*). Anticoagulant therapy was given to 5 patients with DVT. One patient with DVT developed acute respiratory distress and died within 24 hr. An autopsy was not performed. Only one patient (0.2%) developed symptomatic PE, which occurred 8 wk after the initial scan.
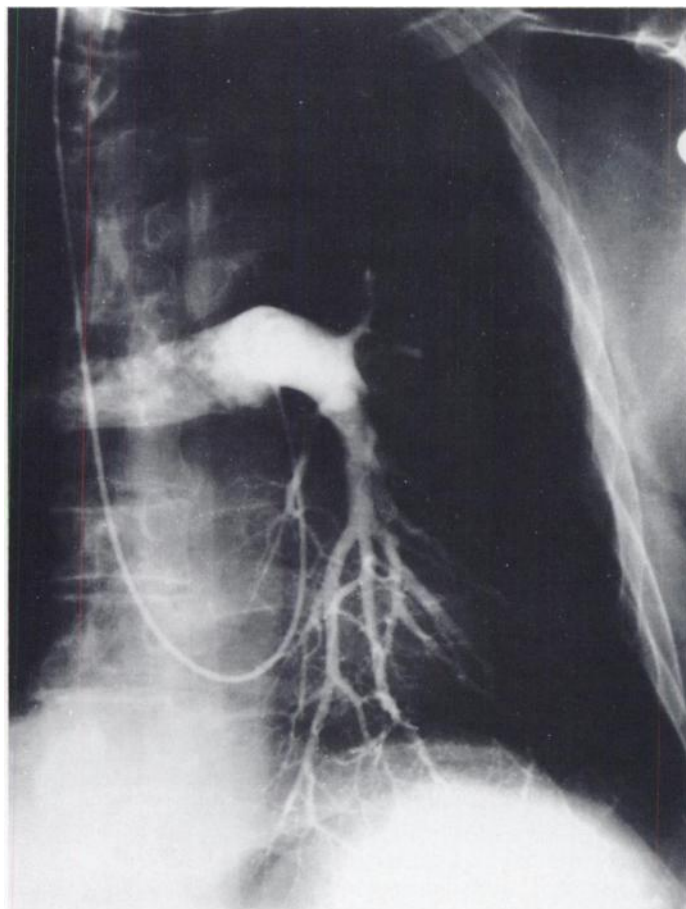
Lung Scan Reporting

The method of reporting lung scan findings requires careful consideration. One issue to consider is whether the lung scan should be reported with or without incorporating the pretest clinical probability of PE. If the probability of PE is estimated from the lung scan without clinical data, the referring clinician should incorporate the pretest probability estimate to form a final impression. One study, however, showed that most referring clinicians use the lung scan result to guide therapeutic management and disregard the pretest clinical probability (*15*). The best approach may be to report the lung scan findings based on specified criteria and consult with the referring clinician to determine final estimate of probability. Pretest clinical suspicion, as shown by the PIOPED data, makes a significant difference in the final predictive value of the lung scan. The incidence of PE was 96% in patients with high clinical suspicion and a high probability lung scan, whereas the incidence of PE was only 4% in patients with low clinical suspicion and a low probability lung scan (*9*).

A second issue is the use of terminology. The interpretation of probability language varies widely among nuclear medicine practitioners. The terms "medium" and "intermediate," which are synonymous, are often confused with "indeterminate." Indeterminate should be reserved for studies in which an estimate of probability cannot be given because of technical limitations. The use of a numerical estimate of probability or likelihood ratio has been recommended (*12,16*). It has also been recommended that lung scans should be reported as normal, high probability or nondiagnostic because of the incidence of PE in the low probability category, and interobserver variability in classifying scintigrams as low or intermediate probability (*17–18*).

TABLE 1
V/Q Criteria for Categorizing Probability of PE

Probability of PE	Sullivan (7) (based on McNeil)	Biello (8)	PIOPED (9)	Revised PIOPED (10)
Normal	No Q defects	No Q defects	No Q defects Q outlines exactly the shape of the lungs on CXR	No Q defects Q outlines exactly the shape of the lungs on CXR
Very low			≤3 small Q defects with normal CXR	
Low	Multiple V/Q matches Single subsegmental V/Q mismatch	Small V/Q mismatches V/Q matches without corresponding CXR changes Q defect CXR≪ density	Nonsegmental Q defect 1 mod V/Q mismatch, with normal CXR Q defect ≪CXR Large or mod V/Q matches, involving ≤4 segments in 1 lung and ≤3 segments in 1 lung region with normal CXR or findings ≪Q defects >3 small Q defects with normal CXR	Nonsegmental Q defect Any Q defect ≪CXR abnormality V/Q matches provided that there are clear CXR and some areas of normal perfusion in the lungs* Any number of small Q defects with a normal CXR
Intermediate	Q defect with matched density on CXR Mixed V/Q mismatches and matches Single segment, lobe or lung V/Q mismatch Multiple subsegmental V/Q mismatches	Severe diffuse OPD with Q defects Single medium or large V/Q mismatch Q defect same size as CXR change	Anything not falling into normal, very low, low, or high probability categories Borderline high or borderline low Difficult to categorize as low or high	1 mod to 2 large V/Q mismatches or the arithmetic equivalent in moderate or large and moderate defects† Single V/Q match and normal CXR Difficult to categorize as low or high, or not described as low or high
High	Multiple segmental or larger V/Q mismatches	≥2 medium or large V/Q mismatches Q defect ≫CXR density	≥2 large V/Q mismatches, with normal CXR or findings ≪Q defects ≥2 mod V/Q mismatches and 1 large V/Q mismatch without CXR findings ≥4 mod V/Q mismatches without CXR findings	≥2 large V/Q mismatches or the arithmetic equivalent in moderate or large and moderate defects†

*Very extensive defects can be categorized as low probability. Single V/Q matches are borderline for low probability and thus should be categorized as intermediate in most circumstances by most readers, although individual readers may correctly interpret individual scans with this pattern as showing low probability.

†Two large V/Q mismatches are borderline for high probability. Individual readers may correctly interpret individual scans with this pattern as showing high probability for PE. In general, it is recommended that more than this degree of mismatch be present for inclusion in the high probability category.

V = ventilation; Q = perfusion; CXR = chest radiograph; OPD = obstructive pulmonary disease; ≪ = substantially smaller than; ≫ = substantially larger than; nonsegmental Q defect = very small effusion, cardiomegaly, enlarged aorta, hila or mediastinum, elevated diaphragm. Biello criteria: small = <25% of a segment; medium = 25%–90% of a segment; large = >90% of a segment. PIOPED criteria: small = <25% of a segment; moderate = 25%–75% of a segment; large = >75% of a segment.

Noninvasive Studies of the Legs

PE is a complication of DVT and not a distinct disease entity. More than 90% of pulmonary emboli originate in the legs (19). Evaluation of the legs for DVT can be helpful if the combination of clinical suspicion and lung scan are not sufficient for the diagnosis of PE. Hull et al. studied 414 patients who had suspected PE and a low-to-intermediate probability lung scan using serial impedance plethysmography (IPG) (20). Three hundred seventy-one patients had negative serial IPG and were not receiving anticoagulants. Only 10 patients (2.7%) were documented to have DVT or PE during the next 3 mo. The combination of a low or intermediate probability lung scan and a negative IPG, however, is not sufficient to rule out PE in patients who have a high clinical suspicion of PE.

Recent studies of IPG report a sensitivity of 66%, which is significantly lower than values previously reported (21–22). Ultrasonography has largely supplanted IPG because it is more widely available and more sensitive, especially in asymptom-

atic patients (23). The single criterion of noncompressibility of the vein on gentle pressure with the probe has been shown to be the most accurate method for the detection of DVT (24). In a study comparing ultrasound and IPG in patients with clinically symptomatic DVT, the positive predictive values were reported to be 94% and 83%, respectively (25). Ultrasound may be used as an adjunctive test when clinical suspicion and lung scans are not sufficient for diagnosis of PE. A patient with a low clinical suspicion of PE, nondiagnostic lung scan and normal ultrasonography may not need further testing.

The low cost, convenience and widespread availability of ultrasonography has resulted in some patients with suspected PE having ultrasonography instead of a lung scan. Although 90% of pulmonary emboli originate in the legs, this approach cannot be recommended since 30% of patients with PE have a negative contrast venous study, presumably because the thrombus has embolized (26). Ultrasonography is even less likely to be positive, since DVT below the level of the popliteal vein is not routinely detected. Only 25/51 patients (49%) with clinical suspicion of PE and a high probability lung scan had positive ultrasonography in one recent report (27). Furthermore, only 1 patient had DVT detected by ultrasonography in a subset of 10 patients with PE confirmed by arteriography. A negative lower extremity study for DVT, therefore, does not rule out PE.

A positive ultrasonography examination indicating DVT does not always eliminate the need for a lung scan, even though treatments the DVT and PE are the same. Up to 40% of patients with DVT can have asymptomatic PE (28). It is important to document baseline pulmonary perfusion because 5%–20% of patients with DVT will develop new perfusion defects even with anticoagulation (29). The documentation of new perfusion defects may require a change in treatment or placement of a caval filter.

Pulmonary Arteriography

Pulmonary arteriography remains the gold standard for diagnosing acute PE. Arteriography, however, is invasive and accompanied by certain risks. Minor complications occur in 5% of patients. Major complications, such as respiratory distress requiring resuscitation or intubation, renal failure requiring dialysis and bleeding requiring transfusion, occur in 1%. Death occurs in 0.5% (30). As with any diagnostic imaging modality, performance and interpretation are subject to variability. Among the 1111 patients undergoing pulmonary arteriography in the PIOPED trial, 35 studies (3%) were nondiagnostic, and the study could not be completed in 12 patients (1%) (30). The diagnosis was reversed by the classification committee in 4/681 patients (1%) with negative arteriograms on the basis of autopsies performed within 6 days. Interobserver agreement on whether PE was present, absent or uncertain was 81% ± 2% in technically adequate studies (30). Interobserver agreement is higher in negative studies when arteriograms are of high quality. Agreement is higher in positive studies when emboli are large and located proximally (30).

Other Imaging Modalities

Emboli in proximal pulmonary arteries can be detected by helical CT, although the examination still requires intravenous radiographic contrast. Helical CT studies eliminate respiratory misregistration in patients who can hold their breath, although diagnostic studies can usually be obtained in patients who cannot cooperate. Electron beam CT scans can be performed in 100 msec, which eliminates the need for breath-holding, but the technology is expensive and available at only a few centers. The resolution limits for small emboli are unknown with either modality. The reported sensitivities are high when compared to

arteriography (31). Wide clinical use awaits a large study that includes outcome analysis to confirm this observation.

MRI using standard and angiographic sequences can detect central pulmonary emboli (32). MRI is limited by availability and difficulty in monitoring unstable patients in the magnet. Again, a definitive, limiting vessel size for resolving emboli is not documented.

Transesophageal echocardiography can also detect proximal pulmonary emboli and can be used to monitor hemodynamic responses in a less invasive fashion (33).

Other Diagnostic Tests

Plasma D-dimer measurement may be used as an adjunctive test in the diagnosis of PE (34,35). D-dimer is a specific breakdown product released into the circulation by endogenous fibrinolysis of a cross-linked fibrin clot. A high concentration of D-dimer can be found in patients with DVT, PE, acute myocardial infarction and unstable angina. A high D-dimer level, however, is not specific for PE. If the proper threshold is chosen, however, the negative predictive value of plasma D-dimer measurement for acute PE is very high. Plasma D-dimer levels were measured in 173 patients who had pulmonary arteriography for suspected PE (36). Only 3/35 patients with D-dimer values <500 ng/ml had PE. The negative predictive value of a plasma D-dimer level <500 ng/ml for acute PE was 91.4% (95% confidence interval, 76.9%–98.2%). The combination of plasma D-dimer measurement and lower extremity ultrasound can reduce the requirement for pulmonary angiography by one-third among patients with suspected PE and an abnormal but not high probability lung scan (37).

CONCLUSION

Lung scanning remains pivotal in the diagnosis of PE. It is widely accepted that a normal lung scan excludes clinically significant PE and that a scan showing multiple segmental perfusion abnormalities with normal ventilation is diagnostic. The choice of interpretive criteria remains controversial. The gestalt impression of an experienced reader may be more accurate than the application of fixed criteria. A major controversy concerns the reporting of abnormal but not high probability lung scans. The probability of PE can be estimated or the study may be reported as nondiagnostic. If the probability is estimated, the incorporation of a clinical probability estimate improves the final predictive value of the scan. Patients with low clinical suspicion of PE and a low probability scan may be followed without anticoagulation. Patients with other combinations of findings require further investigation. A negative noninvasive lower extremity study may be adequate to justify observation without anticoagulation. A low plasma D-dimer level adds more support to a negative diagnosis. If the clinical suspicion is high, as with the patient in this report, a pulmonary arteriogram is necessary for diagnosis.

REFERENCES

1. Hull RD, Raskob GE, Hirsh J. Prophylaxis of venous thromboembolism: an overview. Chest 1986;89:374S–383S.
2. Lotke PA, Ecker ML, Alavi A, Berkowitz H. Indications for the treatment of deep venous thrombosis following total knee replacement. J Bone Joint Surg 1984;66-A: 202–208.
3. Merli GJ. Update: deep vein thrombosis and pulmonary embolism prophylaxis in orthopedic surgery. Med Clin North Am 1993;77:397–411.
4. Bell WR, Simon TL, DeMets DL. The clinical features of submassive and massive pulmonary emboli. Am J Med 1977;62:355–360.
5. Biello DR, Mattar AG, McKnight RC, Siegel BA. Ventilation-perfusion studies in suspected pulmonary embolism. Am J Roentgenol 1979;133:1033–1037.
6. McNeil BJ. Ventilation-perfusion studies and the diagnosis of pulmonary embolism: concise communication. J Nucl Med 1980;21:319–323.
7. Sullivan DC, Coleman RE, Mills SR, Ravin CE, Hedlund LW. Lung scan interpretation: effect of different observers and different criteria. Radiology 1983;149:803–807.

8. Biello DR. Radiological (scintigraphic) evaluation of patients with suspected pulmonary thromboembolism. *JAMA* 1987;257:3257-3259.

9. The 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.

10. Webber MM, Gomes AS, Roe D, LaFontaine RL, Hawkins RA. Comparison of Biello, McNeil and PIOPED criteria for the diagnosis of pulmonary emboli on lung scans. *Am J Roentgenol* 1990;154:975-981.

11. Gottschalk A, Sostman HD, Coleman RE, et al. Ventilation-perfusion scintigraphy in the PIOPED study. II. Evaluation of the scintigraphic criteria and interpretations. *J Nucl Med* 1993;34:1119-1126.

12. Sostman HD, Coleman RE, DeLong DM, Newman GE, Paine S. Evaluation of revised criteria for ventilation-perfusion scintigraphy in patients with suspected pulmonary embolism. *Radiology* 1994;193:103-107.

13. Kipper MS, Moser KM, Kortman KE, Ashburn WL. Long term follow-up of patients with suspected pulmonary embolism and a normal lung scan. *Chest* 1982;82:411-415.

14. Hull RD, Raskob GE, Coates G, Panju AA. Clinical validity of a normal perfusion lung scan in patients with suspected pulmonary embolism. *Chest* 1990;97:23-26.

15. Frankel N, Coleman RE, Pryor DB, Sostman HD, Ravin CE. Utilization of lung scans by clinicians. *J Nucl Med* 1986;27:366-369.

16. Gray HW, McKillop JH, Bessent RG. Lung scan reporting language: what does it mean? *Nucl Med Commun* 1993;14:1084-1087.

17. van Beek EJR, Teil-van Buul MMC, Büller HR, van Royen EA, ten Cate JW. The value of lung scintigraphy in the diagnosis of pulmonary embolism. *Eur J Nucl Med* 1993;20:173-181.

18. Hull RD, Raskob GE. Low probability lung scan findings: a need for change. *Ann Int Med* 1991;114:142-143.

19. Moser KM. Venous thromboembolism: state of the art. *Am Rev Respir Dis* 1990;141: 235-249.

20. Hull RD, Raskob GE, Coates G, Panju AA, Gill GJ. A new noninvasive management strategy for patients with suspected pulmonary embolism. *Arch Intern Med* 1989;149: 2549-2555.

21. Anderson DR, Lensing AWA, Wells PS, Levine MN, Weitz JI, Hirsh J. Limitations of impedance plethysmography in the diagnosis of clinically suspected deep-vein thrombosis. *Ann Intern Med* 1993;118:25-30.

22. Ginberg JS, Wells PS, Hirsh J, Panju AA, et al. Reevaluation of the sensitivity of impedance plethysmography for the detection of proximal deep vein thrombosis. *Arch Intern Med* 1994;154:1930-1933.

23. Wheeler HB, Hirsh J, Wells P, Anderson FA. Diagnostic tests for deep vein thrombosis. Clinical usefulness depends on probability of disease. *Arch Int Med* 1994;154:1921-1928.

24. Lensing AWA, Prandoni P, Brandjes D, Huisman PM, et al. Detection of deep-vein thrombosis by real-time B-mode ultrasonography. *N Engl J Med* 1989;320:342-345.

25. Heijboer H, Buller HR, Lensing AWA, Turpie AGG, et al. A comparison of real-time compression ultrasonography with impedance plethysmography for the diagnosis of deep-vein thrombosis in symptomatic outpatients. *N Engl J Med* 1993;329:1365-1369.

26. Hull RD, Hirsh J, Carter CJ, Jay RM, et al. Pulmonary angiography, ventilation lung scanning and venography for clinically suspected pulmonary embolism with abnormal perfusion scans. *Ann Intern Med* 1983;98:891-899.

27. Smith LL, Iber C, Sirr S. Pulmonary embolism: confirmation with venous duplex US as adjunct to lung scanning. *Radiology* 1994;191:143-147.

28. Moser KM, Fedullo PF, LitteJohn JK, Crawford R. Frequent asymptomatic pulmonary embolism in patients with deep venous thrombosis. *JAMA* 1994;271:223-225.

29. Partsch H, Oburger K, Mostbeck A, König B, Köhn H. Frequency of pulmonary embolism in ambulant patients with pelvic vein thrombosis: a prospective study. *J Vasc Surg* 1992;16:715-722.

30. Stein PD, Athanasoulis C, Alavi A. Complications and validity of pulmonary angiography in acute pulmonary embolism. *Circulation* 1992;85:462-468.

31. Remy-Jardin M, Remy J, Wattinne L, Giraud F. Central pulmonary thromboembolism. Diagnosis with spiral volumetric CT with the single-breath-hold technique—comparison with pulmonary angiography. *Radiology* 1992;185:381-387.

32. Grist TM, Sostman HD, MacFall JR, et al. Pulmonary angiography with MR imaging: preliminary clinical experience. *Radiology* 1993;189:523-530.

33. Come PC. Echocardiographic evaluation of pulmonary embolism and its response to therapeutic interventions. *Chest* 1992;101:151S-162S.

34. Bounameaux H, Slosman D, de Moerloose Ph, Reber G. Diagnostic value of plasma D-dimer in suspected pulmonary embolism. *Lancet* 1988;628-629.

35. Bounameaux H, Cirafici P, de Moerloose P, et al. Measurement of D-dimer in plasma as a diagnostic aid in suspected pulmonary embolism. *Lancet* 1991;337:196-200.

36. Goldhaber SZ, Simons GR, Elliott CG, et al. Quantitative plasma D-dimer levels among patients undergoing pulmonary angiography for suspected pulmonary embolism. *JAMA* 1993;270:2819-2822.

37. Perrier A, Bounameaux H, Morabia A, et al. Contribution of D-dimer plasma measurement and lower-limb venous ultrasound to the diagnosis of pulmonary embolism: a decision analysis model. *Am Heart J* 1994;127:624-635.