Radionuclide Imaging of Acute Pulmonary Embolism

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Pulmonary embolism (PE) is a potentially fatal condition for which treatment is highly effective. The diagnosis of PE can be challenging and often requires diagnostic imaging. For many years, chest radiographs and ventilation-perfusion (V/Q) scintigraphy have been the primary imaging modalities used in the evaluation of patients with suspected acute PE. The combination of clinical assessment, plus results of V/Q scintigraphy and a noninvasive venous study of the lower extremities can provide clinicians with the information needed to direct treatment in the majority of patients with suspected PE. More recently, advances in computerized tomography (CT) angiography have allowed for the direct visualization of PE, and this technique has emerged as an important diagnostic test in the evaluation of patients with suspected PE. Proponents suggest that CT angiography should be used as the first line imaging test in patients with suspected PE. Others suggest that V/Q scanning should remain as the first line diagnostic imaging test and that CT angiography should be used in patient's in whom the diagnosis remains uncertain. The combination of CT angiography and CT venography has the potential to provide a single comprehensive study of patients with suspected venous thromboembolism.

PULMONARY EMBOLISM (PE) is a relatively common and potentially fatal disorder for which treatment is highly effective and improves patient survival. The accurate and prompt diagnosis of acute PE requires an interdisciplinary team approach and may be difficult because of nonspecific clinical, laboratory, and radiographic findings.[1-4] The incidence of venous thromboembolism is approximately 1 in 1,000 per year.[5,6] Approximately 10% of patients with PE die within 1 hour of the event.[7] In an autopsy series of 4,077 patients, deep vein thrombosis (DVT) or PE was present in 24%, and in 14%, PE was determined to be the cause of death.[8] For those patients who survive beyond the first hour following PE, treatment with heparin or thrombolytic agents are both effective therapies.[7,9-12] The overall mortality in patients with PE who are untreated has been 30%.[7] Mortality from PE is highest among hemodynamically unstable patients and can be as high as 58%.[13]

In contrast, the correct diagnosis and appropriate therapy significantly lowers mortality to between 2.5% and 8%.[9,14] In a meta-analysis of 25 studies, including 5,523 patients, the rate of fatal PE during anticoagulant therapy was 0.4% among those presenting with DVT and 1.5% among those presenting with PE.[15] Although anticoagulant therapy is effective for treating PE and reducing mortality, it is not without some risk. The prevalence of major hemorrhagic complications has been as high as 10% to 15% among patients receiving anticoagulant or thrombolytic therapy.[10,13,16-18] In one study investigating drug related deaths among hospital patients, heparin was responsible for the majority of drug related deaths in noncritically ill patients.[19] Therefore, the accurate and prompt diagnosis of PE is not only essential to prevent excessive mortality but also to avoid complications related to unnecessary anticoagulant therapy. With the availability, improved side effect profile of low molecular weight heparin, therapy for PE is often initiated based on clinical presentation, and the diagnosis is later confirmed or excluded by diagnostic imaging.[20]

CLINICAL DIAGNOSIS OF PULMONARY EMBOLISM (PE)

During the clinical evaluation of patients with established PE risk factors, clinical signs and symptoms were similar in males and females.[21] Men have a slightly higher mortality from PE compared with women (hazard ratio 1.7).[22] The risk of PE does increase with age.[23,24] Sedentary lifestyle, prolonged recovery phase following illness, congestive heart failure, malignancy, and increased hip fracture rates in the elderly are factors that increase the likelihood of pulmonary embolism. The clinical findings of patients with suspected PE and no preexisting cardiac or pulmonary disease were evaluated in a subset of the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study population.[25] The most common symptoms of patients with PE and no preexisting cardiac or pulmonary disease were dyspnea, pleuritic chest pain, and cough.[25] However, the prevalence of these symptoms was not significantly different when compared with patients in whom PE was excluded. Dyspnea, tachypnea, or pleuritic chest pain alone or in combination were present in 97% of patients with PE.[24]

Like the symptoms, the clinical signs associated with acute PE are also nonspecific. The prevalence of tachypnea, tachycardia, and fever were similar among patients with PE when compared with those in whom the disease

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was excluded. Increased intensity of the pulmonic component of the second heart sound was more commonly heard in patients with PE. However, this finding was only present in 23% of patients and presumably represents a subset of patients with a high pulmonary clot burden.[25] The prevalence of immobilization (ie, strict bed rest for more than 3 continuous days) and surgery (ie, an incision under regional or general anesthesia) within 3 months were more common in patients with PE compared with those without.[25] The frequency of other risk factors that were recorded during the PIOPED study was approximately the same between the 2 groups.

Neural networks have been also developed to assist in the clinical diagnosis of PE. In simplistic terms, neural networks are computer programs that are capable of processing information similar to the way the human brain processes information. A more detailed description of the application of neural networks in radiologic diagnoses can be found elsewhere.[26] A neural network for the clinical diagnosis of PE has been developed using 50 variables that were available from patients enrolled in the PIOPED study.[27] These variables included information obtained from history, physical examination, chest radiograph, electrocardiograph, and room air arterial blood gas measurements. The likelihood of PE based on clinical findings, as predicted by the neural network, was similar to that predicted by experienced clinicians. Therefore, neural networks can provide a reproducible assessment of the clinical likelihood of PE and may assist in the diagnostic evaluation of patients suspected of having acute PE. However, the clinical manifestations of PE were quite variable and lack the specificity to reliably diagnose or exclude clinically significant PE.

D-dimer

D-dimer is a plasmin mediated degradation product of circulating cross-linked fibrin. An increased D-dimer level is not specific for venous thromboembolism, and may occur in any condition in which fibrin has been formed and degraded by plasmin. Arterial thrombosis disseminated intravascular coagulation, infections, sepsis, recent trauma, and postoperative states may all cause increased D-dimer levels. D-dimer levels are commonly measured using either latex agglutination or enzyme-linked immunosorbent assay (ELISA) based methods. The ELISA based methods are more sensitive and can detect D-dimer concentration levels as low as 30 ng/mL. The latex agglutination method is a more rapid, semiquantitative test that can detect D-dimer concentration levels in the 200 to 500 ng/mL range. The main value of a D-dimer assay is to exclude PE in patients with negative results. The relatively low specificity of the test limits its value in confirming the diagnosis of PE.[28] In a consensus statement from the American College of Chest Physicians there was general agreement that an ELISA based assay that measures D-dimer excluded PE in 90% to 95% of patients, and that a normal latex agglutination D-dimer was unreliable for excluding PE and should not be performed.[29]

In an evaluation of a rapid, bedside agglutination assay ("SimpliRED") in patients in the emergency room, the test had a negative predictive value of only 81%.[30] It was concluded that a negative simpliRED D-dimer assay does not exclude the diagnosis of DVT or PE in patients presenting to the emergency room. The combined use of the SimpliRED semiquantitative assay and the clinical likelihood of disease had a higher sensitivity for diagnosing PE compared with either test alone.[31] There are currently no methods to standardize D-dimer results from different manufactures, and high variations in assay results have been reported.[32,33] To overcome the problems of a low specificity, it has been recommended that the test be performed only on outpatients and used to exclude the diagnosis of PE. Despite this procedure, a meta-analysis of 29 D-dimer studies concluded that the clinical use of the D-dimer assay remains unproven.[34]

Chest Radiographic Findings in Pulmonary Embolism (PE)

Chest radiographs are helpful for excluding diseases that clinically mimic PE and are performed in virtually all patients with suspected PE. In the PIOPED study, chest radiographs were obtained within 24 hours of angiography and among patients with angiographically documented PE.[35] Only 12% (45 of 383) of patients had chest radiographs interpreted as normal. The positive and negative predictive values of a normal chest radiograph were 18% and 74%, respectively. Of patients with PE and no preexisting cardiac or pulmonary disease, only 16% had chest radiographs interpreted as normal.[25] Patients with abnormal chest radiographs are more likely to have intermediate lung scan interpretation compared with patients with a normal chest radiograph. The most common chest radiographic findings in patients with PE were atelectasis and/or parenchymal opacities in the affected lung zone.[25,35] However, atelectasis and/or parenchymal opacities were also the most common finding in patients in whom PE was excluded. Pleural effusions within the affected hemithorax occurred in approximately 35% of patients with PE. Of the patients with PE, the majority of pleural effusions were small, causing only blunting of the costophrenic angles.[35] Although chest radiographic findings alone were nonspecific for PE, chest radiographs are essential for the evaluation of patients with suspected PE to diagnose conditions that can clinically mimic PE and assist in the interpretation of the ventilation-perfusion (V/Q) lung scans.

VENTILATION-PERFUSION (V/Q) LUNG SCANNING IN PULMONARY EMBOLISM (PE)

The V/Q lung scan has been a safe, noninvasive technique to evaluate regional pulmonary perfusion and ventilation. The technique has been widely used for the evaluation of patients with suspected PE. The technique for performing V/Q scintigraphy has been described in detail elsewhere.[36] When performing perfusion scintigraphy, it is recommended to reduce the number of particles in pediatric patients, patients with known right to left shunts, those with pulmonary hypertension, or those who have undergone pneumonectomy or single lung transplantation. A minimum of 60,000 particles are required to obtain an even distribution of activity within the pulmonary arterial circulation and avoid potential false-positive interpretations.[37] We routinely inject 100,000 to 200,000 particles of Tc-99m macro-aggregated albumin (MAA) when performing perfusion scintigraphy in patients with known pulmonary hypertension or in those who have undergone single lung transplantation. Animal studies have shown that perfusion imaging will detect more than 95% of emboli that completely occlude pulmonary arterial vessels more than 2 mm in diameter.[38] Despite imaging in multiple projections, the perfusion scan may underestimate perfusion abnormalities. A solitary, segmental perfusion defect within the medial basal segment of the right lower lobe is completely surrounded by normal lung. Consequently, a perfusion defect in this segment will not be detected on planar perfusion imaging.[39,40]

Perfusion scintigraphy is sensitive but not specific for diagnosing pulmonary diseases. Virtually all parenchymal lung diseases, including tumors, infections, chronic obstructive pulmonary disease, or asthma, can cause decreased pulmonary arterial blood flow within the effected lung zone. Consequently, shortly after the introduction of perfusion scintigraphy, ventilation imaging was combined with perfusion scintigraphy to improve the diagnostic specificity for diagnosing PE. The pathologic basis for combining ventilation and perfusion scintigraphy was that PE characteristically causes abnormal perfusion with preserved ventilation (mismatched defects) (Fig 1), while parenchymal lung disease would most often cause ventilation and perfusion abnormalities in the same lung region (matched defects) (Fig 2). Conditions in which the ventilation abnormality appears larger than the perfusion abnormality (reverse mismatch) include airway obstruction, mucous plug, airspace disease, atelectasis, or pneumonia (Fig 3). Patients with metabolic alkalosis, limited pulmonary vascular reverse, or those treated with inhaled albuterol may also have failure or inhibition of hypoxic pulmonary vasoconstriction, which results in reverse mismatch.

Perfusion imaging can provide an estimate of the pulmonary clot burden and the hemodynamic effects of PE. In addition, perfusion imaging can also identify patients with a patent foramen ovale and increased right heart pressures that are at risk for paradoxic embolization (Fig 4). The majority of patients with acute PE, either completely lyse their thrombus or partially recanalize their pulmonary arteries. Resolution of PE will depend on several factors, including pulmonary clot burden, type and timing of therapy, patient cardiopulumonary status, and age.[41,42] In the urokinase pulmonary embolism trial (UPET), approximately 75% to 80% of perfusion defects resolved by 3 months. Perfusion defects that do not resolve by 3 months remain largely persistent when followed for 1 year (Fig 5).[41,43] The amount of clot resolution observed in the UPET was likely underestimated because ventilation scanning was not performed, and many of the unresolved perfusion defects might have been due to preexisting chronic obstructive lung disease.

In a multicentered study assessing recovery of pulmonary perfusion following treatment with low molecular weight heparin, residual perfusion defects were present in 66% of patients at 3 months.[43] The defect size at 7 to 10 days following the initiation of therapy was a good predictor of defect size at 6 months.[42] Menendez and coworkers have developed a mathematical model to predict the recovery of pulmonary perfusion following PE.[44] The American College of Chest Physicians consensus statement recommends performing a follow-up V/Q lung scan at 3 months following the initial diagnosis to evaluate clot resolution and serve as a baseline for future comparisons.[29,45] If patients are unable to return in 3 months, a V/Q scan at discharge or 7 days following the initiation of anticoagulant therapy may also be useful.

Radiolabeled Peptide Imaging

More recently, there has been considerable interest in antibody fragments and radiolabeled peptides directed against glycoprotein (GP) IIb/IIIa receptors on the surface of activated platelets.[46-50] The Food and Drug Administration has approved “Acutetec,” a Tc-99m labeled synthetic peptide that binds to the GP IIb/IIIa receptors for evaluation of patients with suspected DVT. The main advantage of this agent is its ability to distinguish between acute and chronic DVT. Several Tc-99m labeled peptides directed against activated platelets are currently under investigation for the evaluation of patients with suspected PE (Fig 6). Radiolabeled peptide imaging has the potential to provide a single comprehensive evaluation of patients with venous thromboembolism. However, currently, further studies and the development of newer radiopharmaceuticals are required to realize fully this potential.

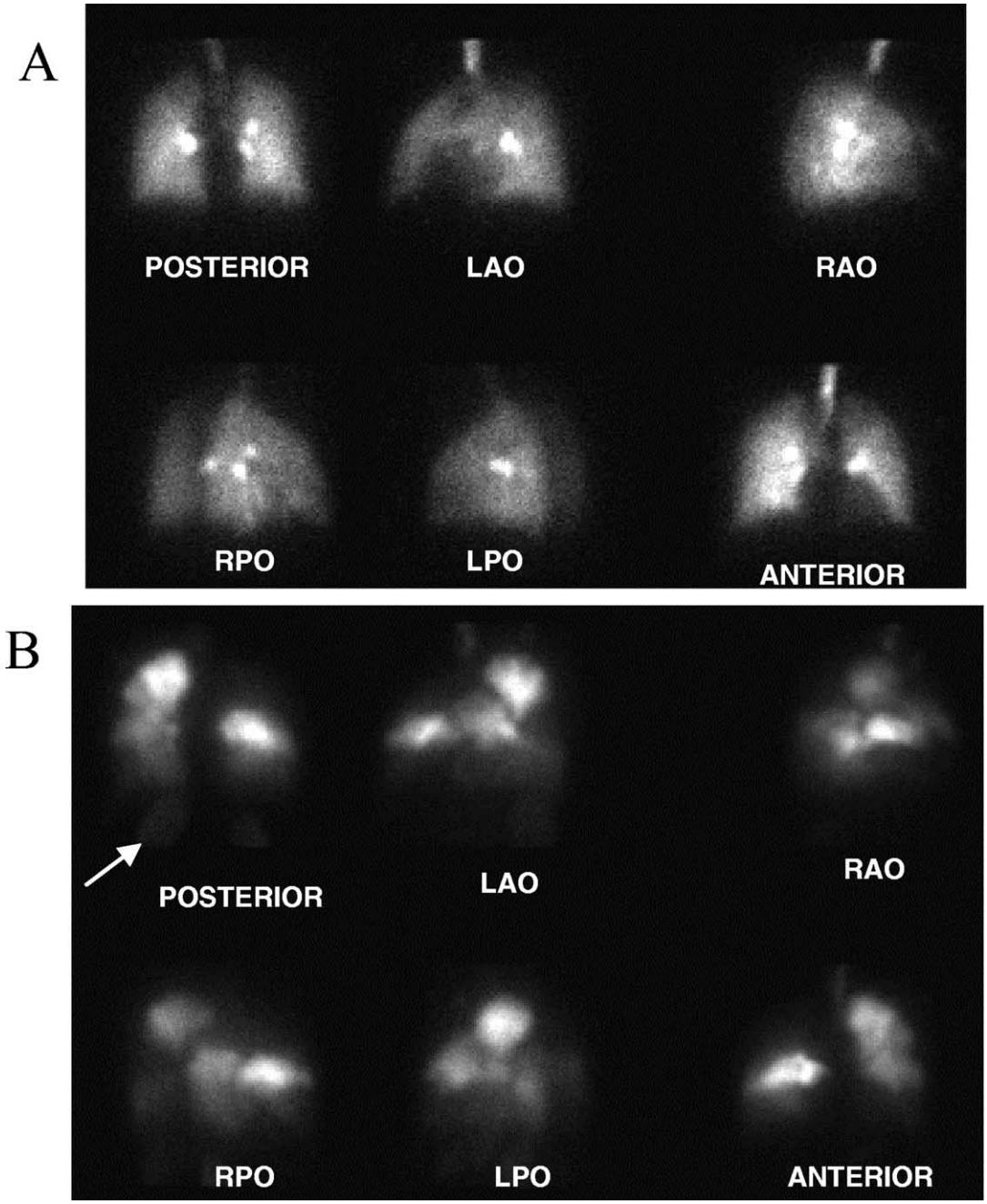

Fig 1. Tc-99m pentetic acid aerosol (A), and Tc-99m macro-aggregated albumin (MAA) perfusion (B) images show multiple bilateral segmental and subsegmental perfusion defects in regions that are ventilated normally (ventilation-perfusion [V/Q] mismatch). The findings indicate a high probability of acute pulmonary embolism (PE). A faint amount of activity is also present within the renal parenchyma, indicating a right-left shunt.

VENTILATION-PERFUSION (V/Q) SCINTIGRAPHY: PROSPECTIVE TRIALS

Data from multiple prospective and outcome based large studies have reported on the efficacy of V/Q scanning in patients suspected of having acute PE.[51-56] In a prospective study by Hull and coworkers, 874 patients suspected of having PE were enrolled.[51] V/Q scan interpretations were grouped into 3 diagnostic categories: (1) normal, (2) nonhigh probability, and (3) high probability (mismatch defect involving at least 75%

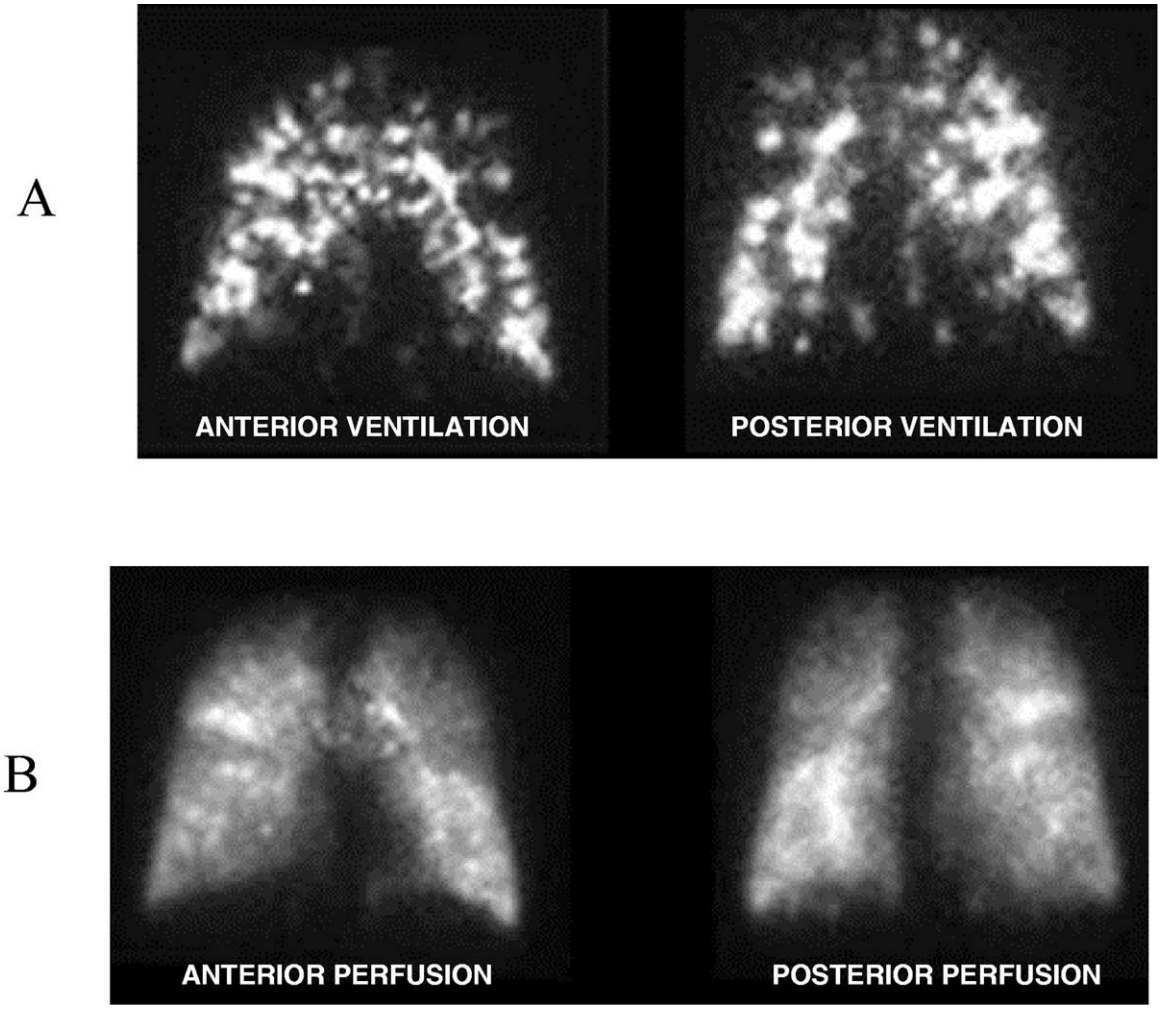

Fig 2. Anterior and posterior Tc-99m pentetic acid aerosol ventilation images (A) showing a marked inhomogeneous distribution of activity within both lungs. There was poor peripheral penetration of activity secondary to turbulent airflow. Tc-99m macro-aggregated albumin (MAA) perfusion images (B) show matching perfusion defects. There were no pleural based regions of ventilation-perfusion (V/Q) mismatch to suggest acute pulmonary embolism (PE). The findings are best explained by chronic obstructive pulmonary disease.

of a segment). The purpose of the study was to determine if anticoagulation therapy could be withheld in patients with a nonhigh probability V/Q scan, adequate cardiorespiratory reserve, and absent proximal vein thrombosis, as determined by negative serial impedance plethysmography (IPG). This diagnostic approach emphasized the importance of the basic pathophysiologic concept that venous thromboembolism is a systemic disease process and that PE was merely the respiratory manifestation of venous thromboembolism. High probability and normal V/Q scans were interpreted in 8% and 36% of patients, respectively. Nine percent of patients had nonhigh probability V/Q scans and inadequate cardiorespiratory reserve defined by the presence of pulmonary edema, right ventricular failure, systolic blood pressure less than 90 mm Hg, syncope, acute tachyarrhythmia, and severely abnormal spirometry or arterial blood gases. Most patients (47%) had nonhigh probability V/Q scans and adequate cardiorespiratory reserve. The outcome in each group was assessed during a 3-month follow-up.

In patients with nonhigh probability lung scan interpretation, adequate cardiorespiratory reserve, and negative serial IPG studies, anticoagulants were withheld. Only 2.7% of these patients had evidence of venous thromboembolism on follow-up. The conclusions from this study were that patients with a nonhigh probability V/Q scan, adequate cardiorespiratory reserve, and negative serial IPG studies could be treated safely without anticoagulation. In addition, these results also confirm

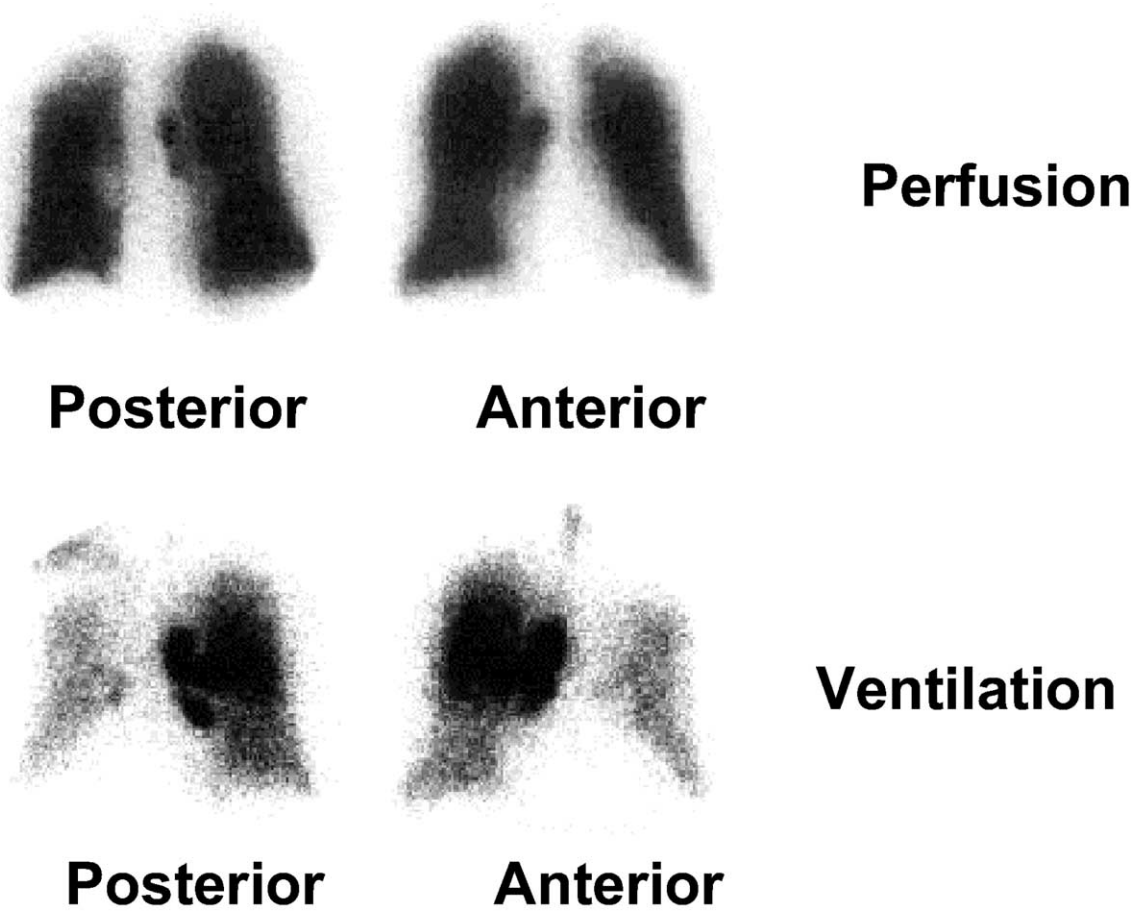

Fig 3. Anterior and posterior Tc-99m pentetic acid aerosol ventilation images showing decreased ventilation within the left lung caused by mucous plugging within the left main bronchus. The Tc-99m macro-aggregated albumin (MAA) perfusion images are relatively normal (reverse mismatch).

findings from previous studies that suggested that the incidence of recurrent PE is very low in the absence of proximal lower extremity venous thrombus. Unfortunately, the interpretation criteria used to categorize the probability of PE (ie, normal, nondiagnostic, or high) were different then those used in the PIOPED study. Consequently, comparison of these results with the PIOPED study is not directly possible.

In a separate study, Hull and coworkers prospectively examined 1,564 consecutive patients with suspected PE who underwent both V/Q scanning and IPG of the lower extremities.[54] In 40% (627) of patients, V/Q scans were interpreted as nondiagnostic, and serial IPG studies were negative. All these patients had an adequate cardiorespiratory reserve and were treated without anticoagulation. Using this algorithm, only 1.9% (12 of 627) had evidence of either DVT or PE on follow-up. Hull and his colleagues have shown that the combination of V/Q scan findings and IPG can be very useful for selecting patients who have not had substantial PE and in whom there is no evidence of proximal lower extremity venous thrombi. In these patients, the risk of recurrent embolic events is low, and anticoagulation may not be required.[14,51,54,57]

Wells and coworkers prospectively examined 1,239 patients with PE.[52] The clinical model categorized pretest probability of PE as low, moderate, or high, and V/Q scanning and bilateral deep venous ultrasound were performed. Using this approach, only 3 (0.5%) of the 665 patients with low or moderate pretest probability and a nonhigh-probability scan had PE or DVT during the 90-day follow-up. Their conclusion was that patients with suspected PE could be safely treated based on pretest probability and results of V/Q scanning.

Perrier and colleagues prospectively examined 1,034 consecutive patients with suspected PE.[53] One hundred and seventy-five patients (21.5%) had a low clinical probability of PE, a nondiagnostic lung scan, negative venous study of the leg, and were not treated with anticoagulants. Of these patients, the prevalence of DVT or PE during follow-up was only 1.7%. These investi-

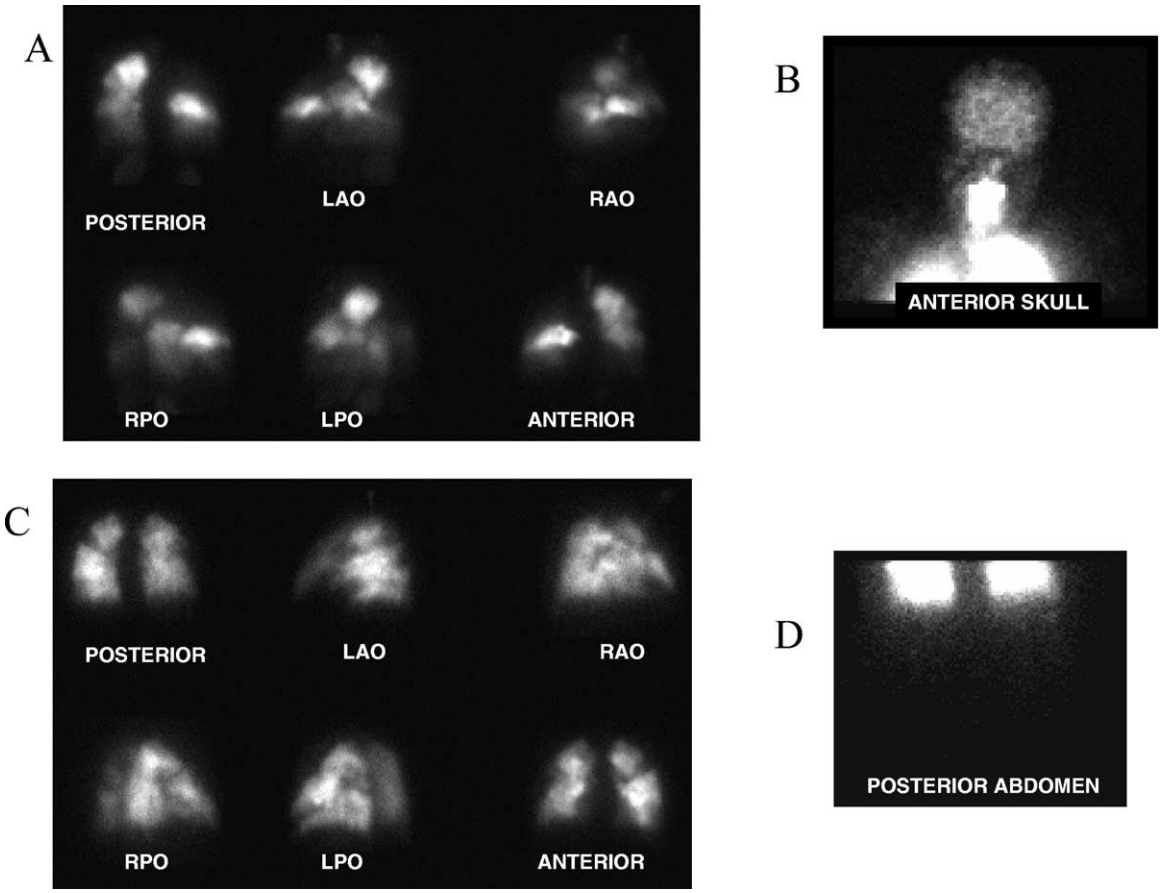

Fig 4. Tc-99m macro-aggregated albumin (MAA) perfusion images (A) showing a high pulmonary clot burden with multiple segmental perfusion defects (same patients as Fig 1). Anterior images (B) of the skull show activity within the brain parenchyma, indicating a right-left shunt, which is likely related to increased right heart pressure and a patent foramen ovale. A follow-up perfusion image (C) 24 hours following thrombolytic therapy shows marked improved perfusion within the right lung and left lower lobe. A posterior image of the abdomen (D) failed to reveal activity within the kidneys, indicating that the increased right heart pressures have decreased and the previously patent foramen ovale has closed.

gators concluded that patients with a nondiagnostic V/Q scan interpretation, low clinical likelihood of PE, and negative venous study of the lower legs could be safely treated without anticoagulation.

Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis (PISA-PED)

In the PISA-PED, which used perfusion scanning alone in conjunction with the chest radiograph, the sensitivity and specificity of scintigraphy was 92% and 87%, respectively.[56] The prevalence in its population was relatively high at 39%. By combining the clinical assessment of the likelihood of PE (ie, very likely, possible, or unlikely), the positive predictive value of a positive perfusion scan was 99%. A near normal or abnormal perfusion scan without segmental defects combined with a low clinical likelihood of PE had a negative predictive value of 97%. Using a standardized clinical assessment and perfusion lung scanning, the investigators of the PISA-PED study have been able to diagnosis or exclude PE with a high diagnostic accuracy (positive predictive value = 96%, negative predictive value = 98%).[58] Only a minority of cases, which had discordant clinical and scintigraphic findings, required computerized tomography (CT) angiography.

Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) Study

To date, the most comprehensive prospective study addressing the role of V/Q scanning in the diagnosis of PE has been the PIOPED study.[55] The PIOPED study was a multi-institutional study designed to evaluate the efficacy of V/Q scanning for diagnosing acute PE. The PIOPED study also provided an opportunity to assess the validity of pulmonary angiography for diagnosing acute

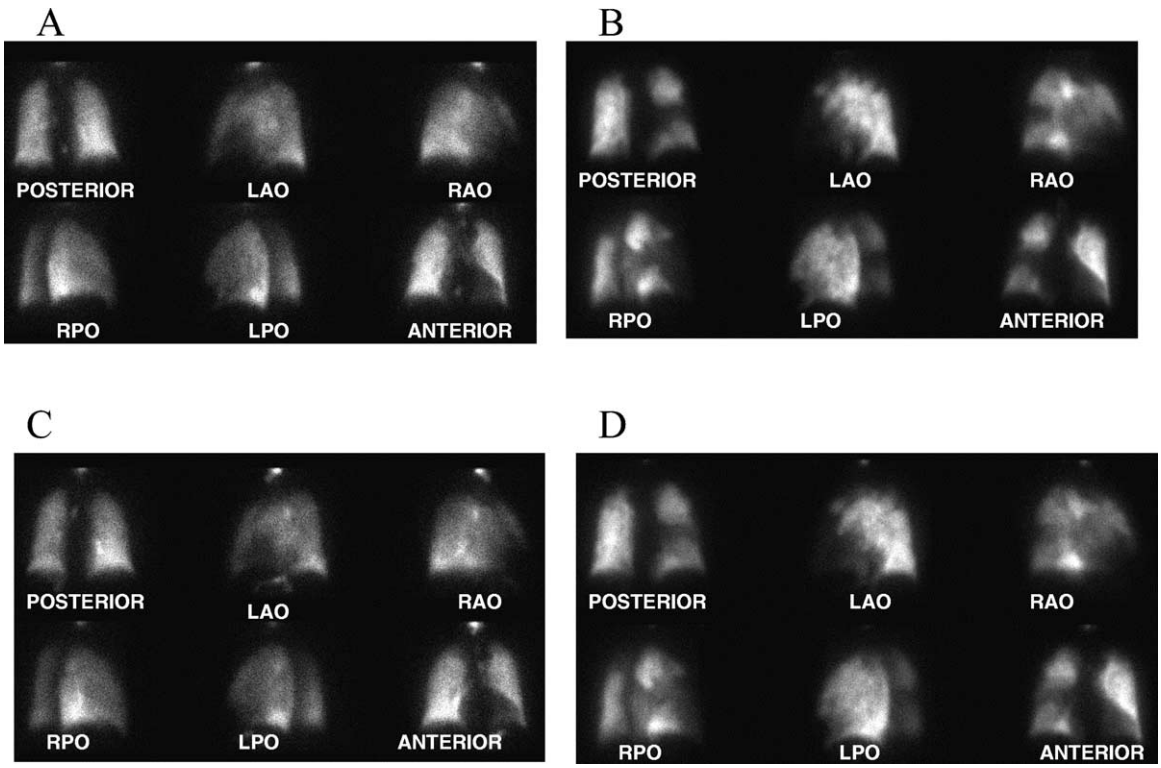

Fig 5. Tc-99m DTPA (A) and Tc-99m macro-aggregated albumin (MAA) perfusion (B) images show multiple bilateral segmental and subsegmental regions of ventilation-perfusion (V/Q) mismatch indicating pulmonary embolism (PE). A follow-up study 3 months later (C, D) was essentially unchanged, confirming chronic, unresolved PE.

PE and determine the incidence of complications related to this procedure.

In the PIOPED study, the sensitivity, specificity, and positive predictive value of a high probability V/Q scan interpretation for detecting acute PE are 40%, 98%, and 87%, respectively. The diagnostic accuracy of V/Q scanning was not significantly different in women compared with men.[21] Similarly, the overall diagnostic performance of the V/Q scan was similar among patients with varying ages.[23,59] The diagnostic use of V/Q scanning for detecting PE was similar in patients with preexisting cardiac or pulmonary disease compared with those with no underlying cardiac or pulmonary disease.[59] In one series that reported on a subset of patients with chronic obstructive pulmonary disease, the sensitivity of a high probability V/Q scan interpretation was significantly lower compared with patients with no preexisting cardiopulmonary disease.[60] However, the positive predictive value of a high probability V/Q scan interpretation was 100%, and the negative predictive value of a low or very low probability V/Q scan

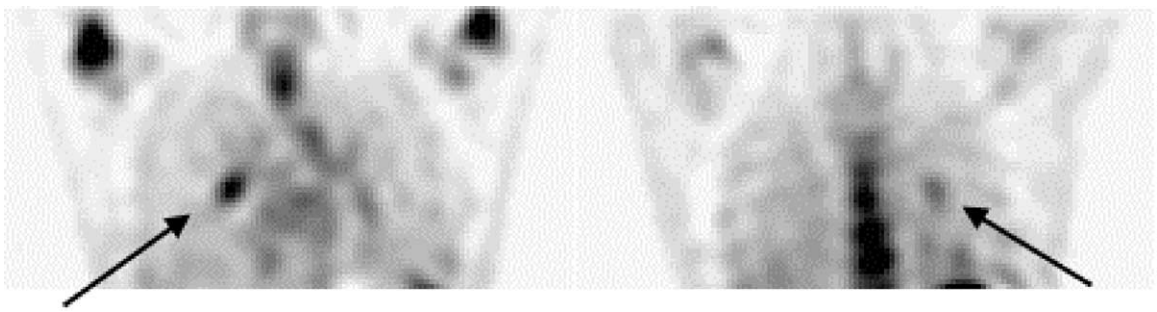

Fig 6. Coronal SPECT images through the mid thorax show increased accumulation of DMP-444 (99mTc-GP IIb/IIIa antagonist) in a patient with documented pulmonary embolism (PE) within the right main and both lower lobe pulmonary arteries.

Table 1. Value of Combining V/Q Scan Interpretation With Selected Risk Factors for Determining the Post Test Likelihood of PE

V/Q Scan Interpretation	0 Risk Factors* No. of Patients with PE/Total No. of Patients (%)	1 Risk Factor* No. of Patients with PE/Total No. of Patients (%)	≥ 2 Risk Factors* No. of Patients with PE/Total No. of Patients (%)
High	63/77 (82)	41/49 (84)	56/58 (97)
Intermediate	52/207 (25)	40/107 (37)	77/173 (45)
Low/very Low	14/315 (4)	19/155 (12)	37/179 (21)
Normal	0/28 (0)	0/7 (0)	0/4 (0)

*Risk factors include immobilization for more than 3 days before presentation, history of surgery, trauma to the lower extremities or central venous instrumentation within 3 months of presentation.

NOTE. Data are from Worsley and Alavi, *J Nucl Med* 36:2380-2387, 1995.

interpretation was 94%. In a more recent study, patients with chronic obstructive pulmonary disease were more likely to have nondiagnostic lung scan interpretations.[61] However, the criteria used to interpret the V/Q studies and time interval between perfusion and ventilation imaging were not provided. Therefore, these results should be interpreted cautiously.

Although the clinical diagnosis of PE is not diagnostic in most instances, the results from the PIOPED study emphasized the importance of incorporating the clinical assessment when evaluating patients suspected of having acute PE. As expected, combining clinical assessment with the V/Q scan interpretation improved the diagnostic accuracy. However, in the PIOPED study, the majority of patients had intermediate probability V/Q scan interpretations and an intermediate clinical likelihood of PE. For these patients, the combination of clinical assessment and V/Q scan interpretation does not provide adequate information to direct accurately patient treatment, and further investigations with peripheral venous studies or CT angiography are usually required.

Ventilation-Perfusion (V/Q) Scanning: Interpretation Pitfalls

One of the problems or pitfalls of V/Q scanning is the interobserver variability. Although there is generally excellent agreement among patients with normal, very low and high probability lung scan interpretations, the interobserver agreement with low and intermediate lung scan interpretation was lower.[55] The use of anatomic lung segment reference charts has reduced interobserver disagreement when interpreting lung scans.[62,63]

Other interpretative pitfalls with V/Q scanning are false-negative and false-positive interpretations. False-negative lung scan interpretations (ie, low probability, PE present) do occur, and patients who have a recent history of immobilization (bed rest for 3 days), recent surgery, trauma to the lower extremities or central venous instrumentation are particularly at risk for this finding. In patients with low or very low probability V/Q scan interpretations and no history of immobilization, recent surgery, trauma to the lower extremities or central venous instrumentation, the prevalence of PE was only 4.5%.[64] As in patients with low or very low probability V/Q lung scan interpretations and one or more than one of the aforementioned risk factors, the prevalence of PE was 12% and 21%, respectively (Table 1). Patients with false-negative lung scan interpretations tend to have nonocclusive subsegmental thrombi, with low pulmonary clot burden. In recent years, concern has been raised that a low probability lung scan interpretation may be misleading and result in unnecessary mortality in patients who have PE and were not anticoagulated. The prognostic value of a low probability lung scan interpretation is excellent, particularly in patients with a low clinical pretest likelihood of disease or negative lower leg ultrasound. In a series of 536 consecutive patients with this finding, there was no evidence that PE was a causative or contributing factor in patients who died within 6 months of imaging.[65]

The most common cause of V/Q mismatch in patients who do not have acute PE is related to chronic or unresolved PE (Fig 5). Other causes of V/Q mismatch in the absence of PE (false-positive V/Q study) include (1) compression of the pulmonary vasculature (eg, mass lesions, adenopathy, and mediastinal fibrosis); (2) vessel wall abnormalities (eg, pulmonary artery tumors, vasculitis) (Fig 7); (3) non-thromboembolic intraluminal obstruction (eg, tumor emboli, foreign body emboli); and (4) congenital vascular abnormalities (eg, pulmonary artery agenesis or hypoplasia). In patients with unilateral V/Q mismatch (ie, hypoperfusion or absent perfusion), within an entire lung or multiple contiguous segments, and normal perfusion in the contralateral lung extrinsic compression of the pulmonary vasculature, congenital abnormalities or proximal PE all need to be considered in the differential diagnosis (Fig 8).[66,67] Patients with a suspected false-positive V/Q scan interpretation or unilateral V/Q mismatch will often require further imaging with CT angiography.

Interpretation Criteria

Several diagnostic criteria, including McNeil, Biello, and PIOPED, have been suggested for the interpretation of V/Q lung scans. In a study comparing the various

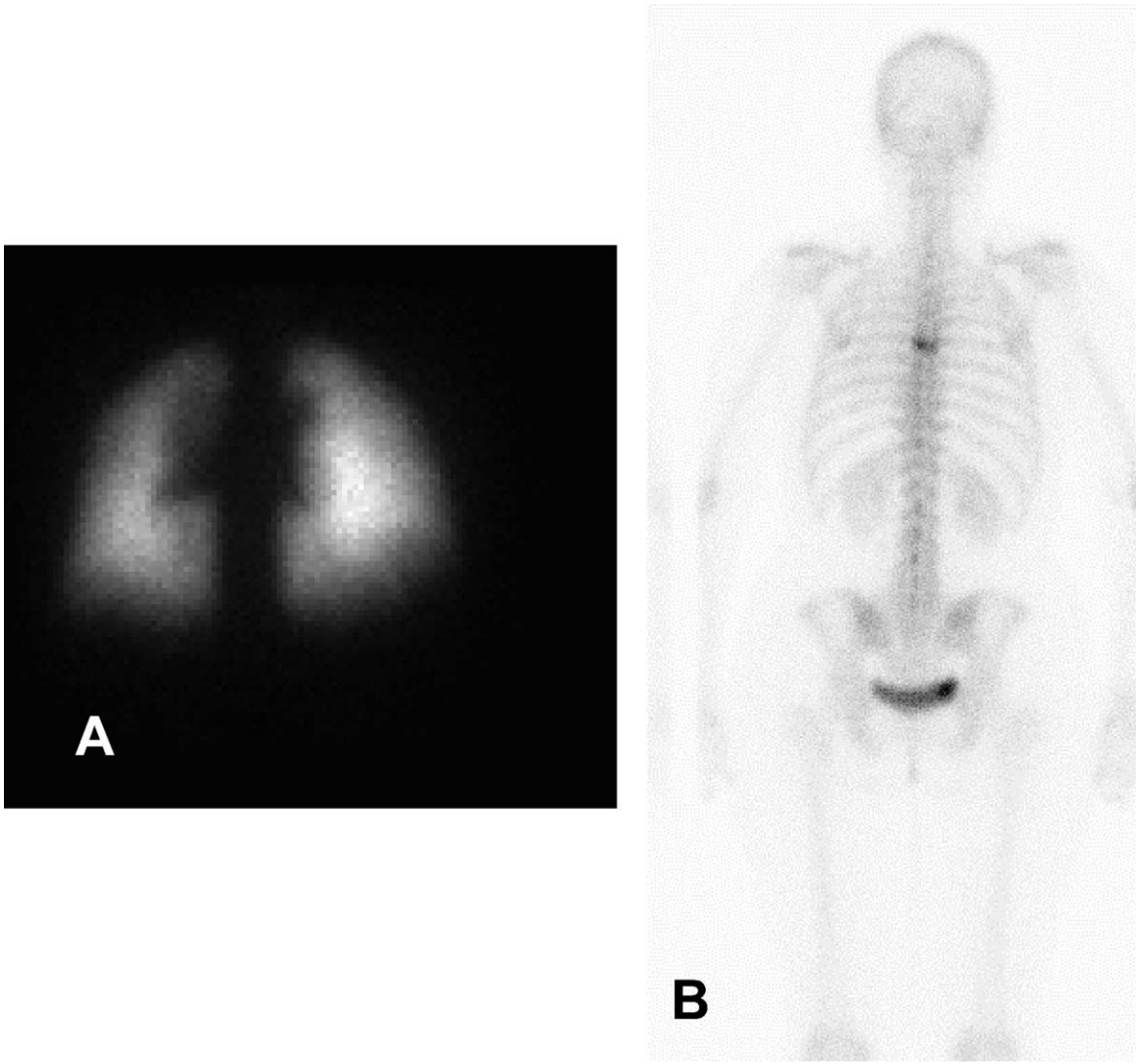

Fig 7. Posterior Tc-99m macro-aggregated albumin (MAA) perfusion image (A) showing decreased perfusion with the medial aspect of both mid lung zones, which is caused by radiation vasculitis in a patient who has recently received radiotherapy for treatment of a solitary bone metastases (B).

interpretation algorithms, the original PIOPED criteria had the highest likelihood ratio for predicting the presence of PE on pulmonary angiography. However, the PIOPED criteria also had the highest proportion of V/Q scans interpreted as representing an intermediate probability of acute PE.[68] Several revisions of the original PIOPED criteria have been made based on the observations from the PIOPED study.[69-73] In PIOPED patients with nonsegmental perfusion abnormalities, perfusion defects, which were smaller than corresponding chest radiographic abnormalities, small subsegmental defects, or patients with a stripe sign on perfusion images all had less than a 10% posttest likelihood of PE.[71,74] In addition, patients with matching V/Q and chest radiographic abnormalities (triple match), which showed decreased rather then absent perfusion, in the middle and upper lung zones were very unlikely (ie, less than 1%) to have PE.[75] Patients with triple matches in the lower lung zones had a posttest prevalence of PE ranging from 18% to 61%, depending on whether perfusion was decreased or absent. By using a number of these revisions, it is possible to decrease the number of intermediate V/Q scan interpretations and correctly interpret them as low probability of acute PE. The use of revised PIOPED criteria has provided a more accurate assessment of angiographically proven PE compared with the original criteria.[71,76-78]

The nuclear medicine physician's subjective estimate of the likelihood of PE (without using specific interpretation

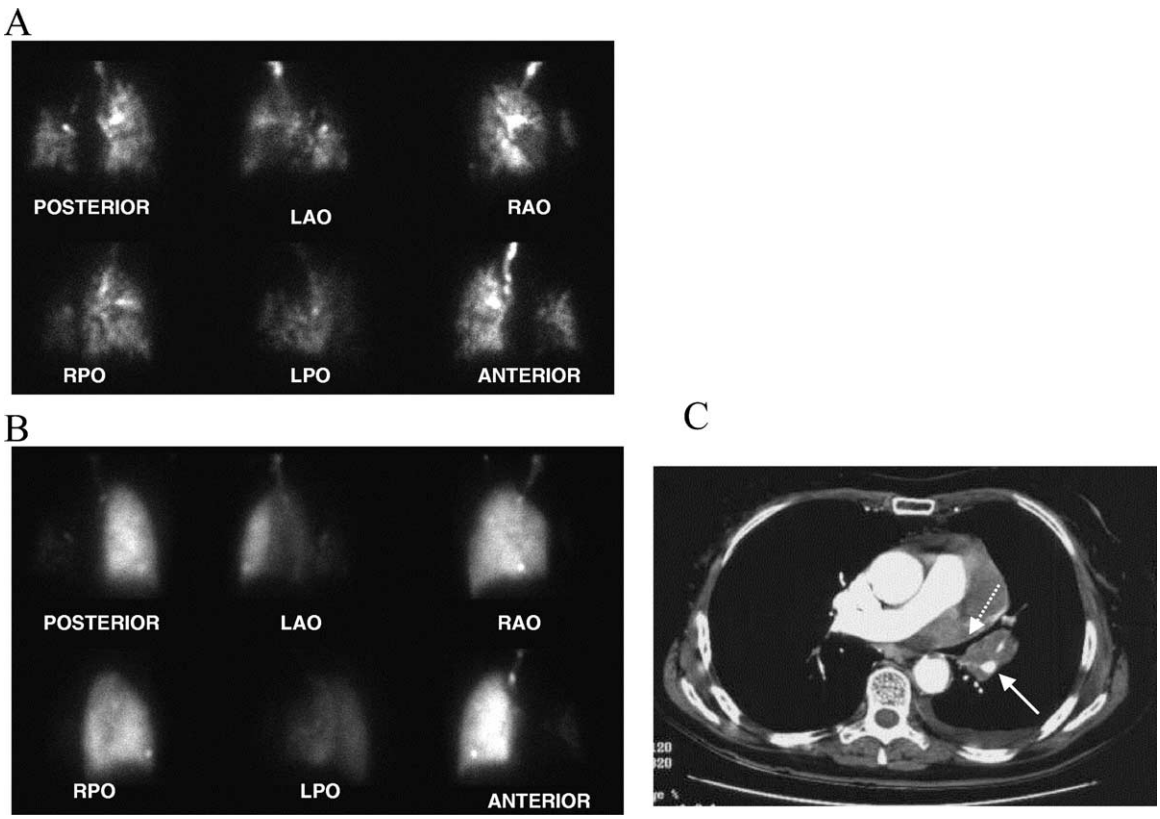

Fig 8. Tc-99m pentetic acid aerosol (A) and Tc-99m macro-aggregated albumin (MAA) perfusion (B) images showing unilateral, markedly decreased activity within the entire left lung. Ventilation within the left upper lung zone is markedly decreased. However, ventilation-perfusion (V/Q) mismatch is present within the left lower lung zone (unilateral V/Q mismatch). A single transaxial slice from the CT angiogram (C) shows a large, left upper lobe mass and associated left hilar adenopathy, which is causing encasement of the left lower lobe pulmonary vasculature (solid arrow). The left lower lobe bronchus (dotted arrow) is compressed but remains patent. Although pulmonary embolism (PE) may rarely present as unilateral V/Q mismatch, the presence of this finding more typically indicates extrinsic compression of the pulmonary artery or vein.

criteria) correlated well with the fraction of patients with angiographic evidence of PE.[77] Experienced nuclear medicine physicians often rely on a complex interaction between information derived from clinical presentation, chest radiographic findings, published criteria, and ancillary findings when interpreting lung scans.[79] Thus, experienced readers, such as the PIOPED investigators, can provide an accurate estimate of the probability of PE based on the clinical, radiographic, and scintigraphic findings. A recent analysis compared the accuracy of neural network and multivariate logistic regression, using 21 variables obtained from scintigraphy and chest radiographs.[80] The diagnostic performance of the complex analytic models was similar to simpler models based on the number of subsegmental mismatches.

CT ANGIOGRAPHY IN PULMONARY EMBOLISM (PE)

Spiral and helical CT angiography, and electron beam CT have been used to visualize directly and diagnose PE. With spiral CT angiography, data are continuously and rapidly collected as the patient moves through the gantry. Volumetric datasets of the entire lungs can generally be acquired during a single breath, which eliminates respiratory misregistration. Electron beam CT is less widely available and has superior temporal resolution but inferior spatial resolution compared with spiral CT. Electron beam CT does not acquire a true volumetric dataset but rather acquires overlapping transaxial images, which can be reformatted to be viewed as multiplanar or 3-dimensional images. In animal models, CT angiography has detected thrombi in central to fourth division (segmental) pulmonary arteries.[81,82] In an animal model, multislice CT angiography is comparable with pulmonary angiography for detecting segmental and subsegmental PE.[83]

The performance of optimum CT angiography for detection of PE is technically demanding, and several examination parameters need to be considered. Scans are generally performed from the level of the aortic arch to

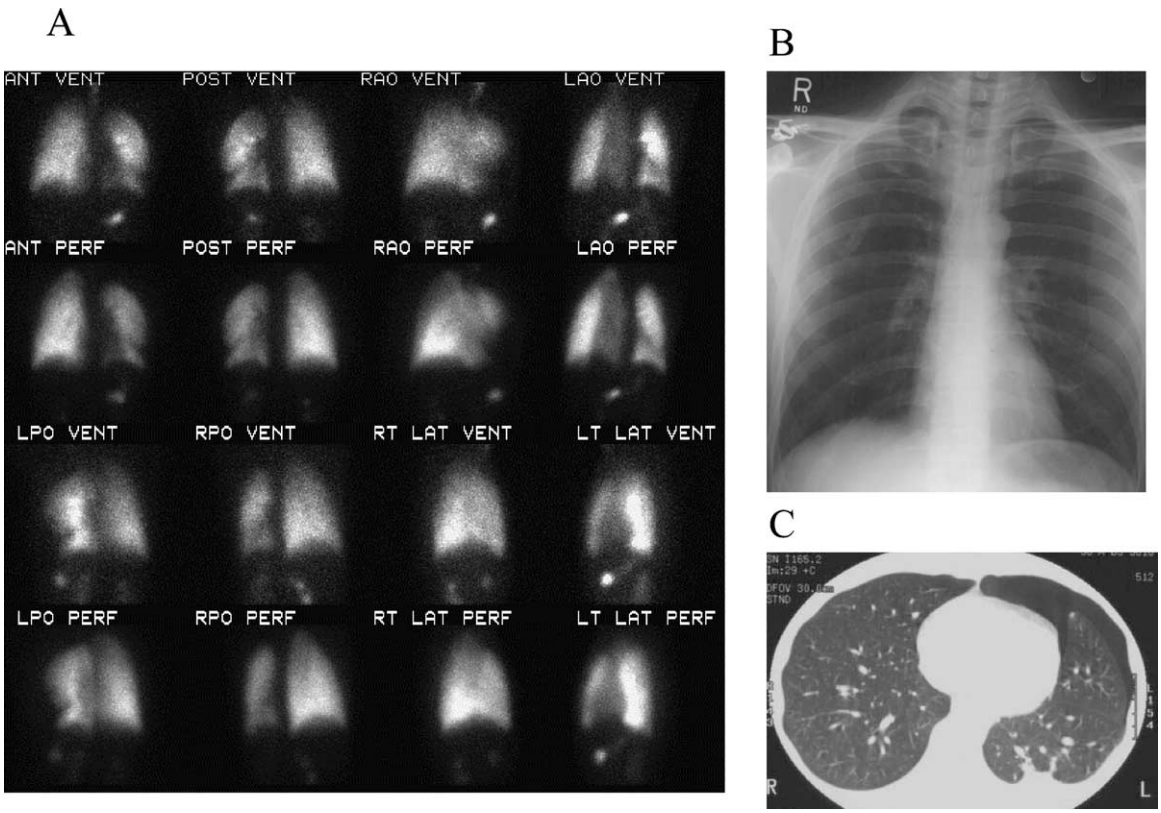

Fig 9. Tc-99m aerosol ventilation and Tc-99m macro-aggregated albumin (MAA) perfusion images of a young male showing generalized, mild matching decreased activity within the left hemithorax. No pleural based regions of ventilation-perfusion (V/Q) mismatch to suggest acute pulmonary embolism (PE) were present. Chest radiograph (B) was interpreted as normal. Single transaxial slice from CT angiogram (C) shows a left pneumothorax with normal opacification of the pulmonary arteries.

below the inferior pulmonary veins. Imaging with multislice scanners can be performed during a single breath hold or during shallow respiration. Scan volumes are generally at least 15 cm and can be performed in either the caudal-cranial or reverse direction. For optimum reporting, images should be viewed on pulmonary vascular and lung parenchymal settings at a workstation.

Depending on the series, the sensitivity and specificity of CT angiography for detecting PE range from 53% to 100% and 75% to 100%, respectively.[84-96] The diagnostic performance of CT angiography for detecting subsegmental thrombi is lower, compared with central PE. In a prospective comparison of spiral CT and pulmonary angiography in 20 patients, Goodman and coworkers reported that the sensitivity for detecting PE decreased from 86% to 63% when all vessels (segmental and subsegmental) were included.[92] Similarly, Teigen and colleagues, using ultrafast CT, showed that the sensitivity for the detection of PE decreased from 88% to 65% when subsegmental vessels were included.[90] In a prospective study comparing spiral CT angiography and V/Q scintigraphy, Mayo and coworkers reported that spiral CT angiography had a higher sensitivity compared with a high probability V/Q scan interpretation.[97] In this study, the specificity, positive predictive value, and negative predictive value were similar between the 2 modalities. A more recent study showed a higher sensitivity and specificity for diagnosing PE with CT angiography, compared with V/Q scanning.[98] CT angiography is more likely to provide an alternative diagnosis in patients who do not have PE (Fig 9).[97,98] Another advantage of spiral CT angiography compared with V/Q scanning is higher interobserver agreement and the ability to provide an alternative diagnosis for patients with suspected PE (Fig 8).[88,97,98]

On CT angiography acute PE appears as an intraluminal filling defect, which partially or completely occludes the pulmonary artery, or as an abrupt vessel cutoff (Fig 10). Commonly, mild vascular distension is present within the effected vessel at the site of the thrombus. Other indirect signs that suggest PE include dilated central pulmonary artery, dilated right ventricle, or wedge shaped consolidation. Segmental pulmonary arteries are located in close

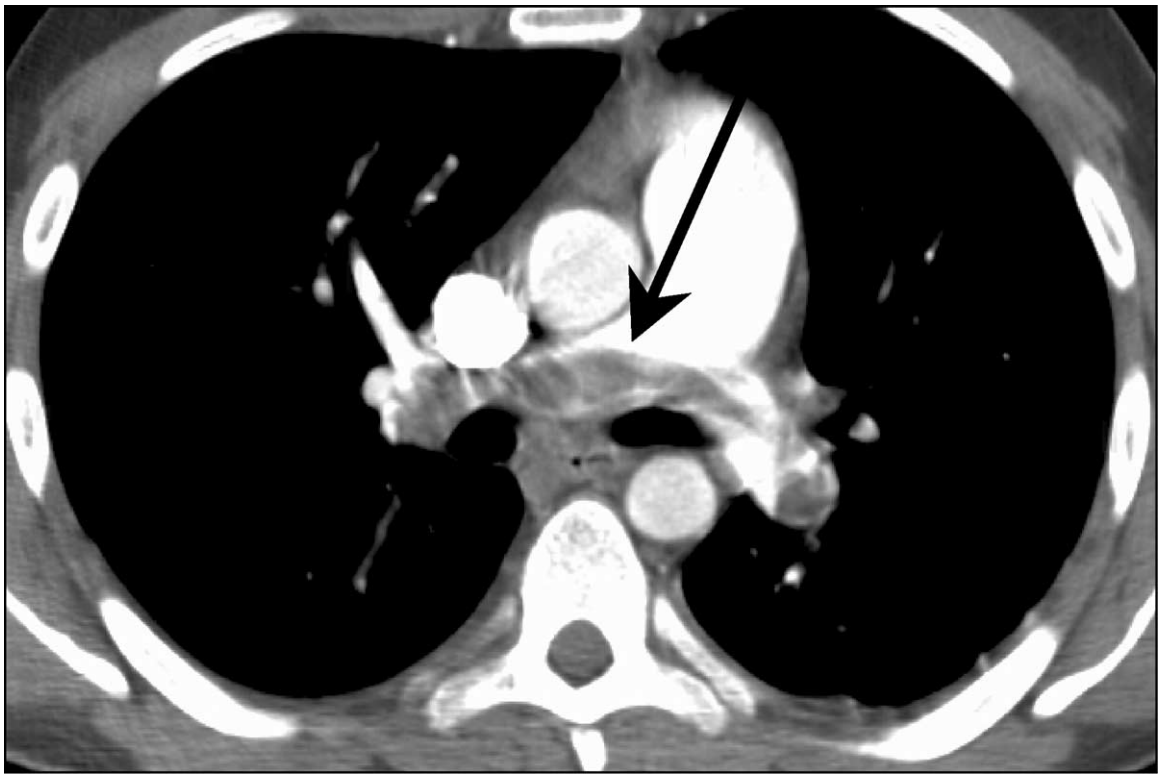

Fig 10. Transaxial CT angiography image showing a filling defect within the main plus proximal left and right pulmonary arteries caused by a large saddle type embolus.

proximity to their accompanying bronchus on the corresponding lung window. Upper and lower lobe arteries run perpendicular to the scan plane, while lingular and right middle lobe arteries tend to run parallel to the scan plane, and in these vessels, the sensitivity for detecting PE may be lower (Fig 11).[89,92,99] Other limitations of CT angiography include technical failures and incomplete examinations.

Patient-related factors that can result in incomplete or suboptimal examinations include orthopnea, poor intravenous access, or severe shortness of breath. In patients who are unable to breath hold, respiratory misregistration may occur and degrade image quality. Poor signal-to-noise ratio or vascular enhancement may occur in patients with right heart failure, large right to left shunts, or extravasated intravenous lines. Intravenous contrast also has to be used cautiously and may be contraindicated in patients with renal insufficiency. An imaging artifact called flow phenomenon, which produces a central low density within the vessels oriented perpendicular to the scan, has been described. This process is most often seen in vessels scanned either too early or too late following intravenous contrast. The mechanisms causing this artifact have not been fully elucidated. However, it is likely due to laminar flow and uneven mixing of contrast within the vessel.[99] Despite the technical demands, CT angiography can provide a prompt and accurate diagnosis of PE in most patients. The prevalence of suboptimal CT angiography examinations depends on the technique used and the population examined. In selected patients, technically inadequate studies occur in approximately 2% to 4% of patients.[100-104] A recent cost-effectiveness analysis has suggested that CT angiography, when used in combination with D-dimer assay or venous study of the legs, can be cost-effective. However, CT angiography, as a single test, was not cost-effective.[105]

In a meta-analysis, CT angiography had a similar positive predictive value as a high probability lung scan interpretation.[106] Other recent meta-analyses on the role of CT angiography in the diagnosis of PE have concluded that CT angiography is sensitive and specific for diagnosing central PE but relatively insensitive for diagnosing subsegmental PE, and the safety of withholding anticoagulant treatment in patients with negative results on CT angiography is uncertain. The authors emphasize that spiral CT for the diagnosis of PE has not been adequately evaluated, and further prospective studies to evaluate the sensitivity, specificity, and the safety of CT angiography are required.[107,108] Since these review papers were published, there have been a number of studies that have specifically evaluated the safety of withholding anticoagulant therapy in patients with a negative CT angiogram.[103,109-113] The

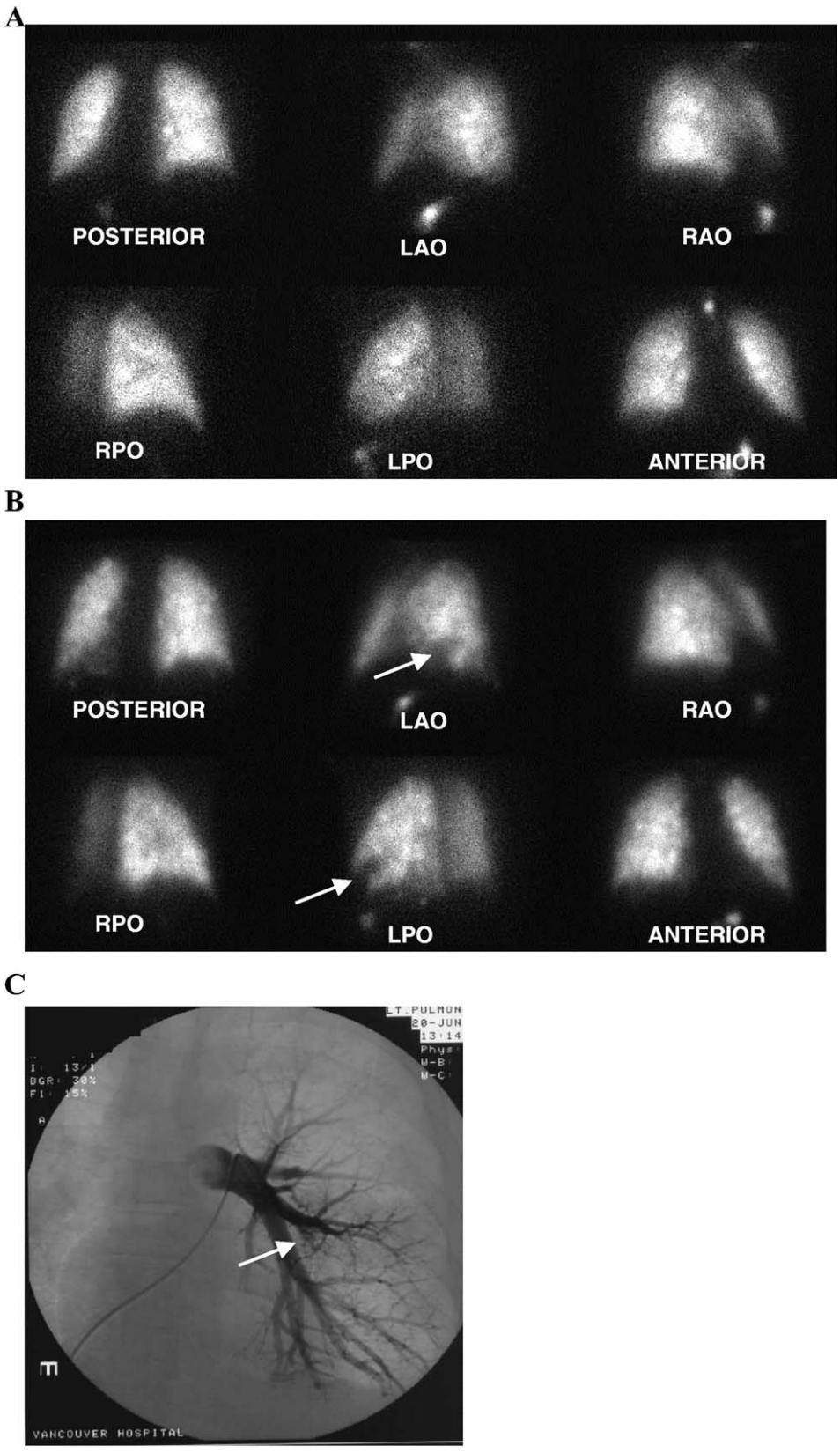

Fig 11. Tc-99m DTPA ventilation (A) and Tc-99m macro-aggregated albumin (MAA) perfusion (B) images show a single segmental ventilation-perfusion (V/Q) mismatch (arrow) within the superior lingular segment in this patient at 3 days postoperatively following surgery for a fractured hip. Matching decreased ventilation and perfusion was also present within multiple segments of the left lower lobe. A spiral CT performed within 1 hour of the V/Q scan was normal. A subsequent pulmonary angiogram (C) showed an intraluminal filling defect and abrupt vascular cutoff within a lingular artery (arrow), confirming pulmonary embolism (PE).

data indicated that, in selected patient populations, CT angiography has a high negative predictive value for excluding PE, and anticoagulant therapy may be safely withheld in selected patients with suspected PE, and a negative CT angiogram and negative venous studies of the legs. In a study of 299 unselected outpatients referred from the emergency department, sensitivity and specificity of CT angiography for detecting PE was 70% and 91%, respectively.[104]

The combination of CT venography and CT angiography was initially described in 1998 and is a particularly attractive technique for the evaluation of patients with suspected venous thromboembolism.[114] In the combined approach, CT images of the inferior vena cava, and pelvic and lower leg vein are performed 2 to 4 minutes following pulmonary CT angiography, and provide a single comprehensive study of patients with suspected PE and/or deep vein thrombosis (DVT). From a clinical and patient outcome point of view, it is likely that hemodynamically stable PE is less important than a silent large thrombus within the pelvic or lower leg veins (Fig 12). The prevalence of isolated DVT in patients with suspected PE varies between 4% and 8%.[114-117] The ability of CT venography to differentiate reliably between acute and chronic DVT is unknown. Orthopedic prosthesis, vascular calcification, or contrast within the urinary bladder may cause beam hardening artifacts and limit the usefulness of CT venography in selected patients.[118] Flow artifact and poor vascular opacification are commonly seen in many patients with peripheral vascular disease, which limits the usefulness of this technique in these patients (Fig 12). Whether or not CT venography should be routinely performed in all patients with suspected PE remains controversial.[114]

The PIOPED II is a multicentered, prospective, outcome based National Heart, Lung and Blood Institute based study designed to assess the accuracy of CT angiography in the evaluation of acute PE.[119] Briefly, PIOPED II will evaluate whether CT angiography can be used as a definitive diagnostic test to replace V/Q scanning and pulmonary angiography. The use of CT angiography in patients with nondiagnostic V/Q scan interpretations, the ability of CT angiography to evaluate subsegmental thrombus, and the negative predictive value of CT angiography will also be evaluated. PIOPED II opened in the fall of 2001 and will recruit approximately 1,100 patients. To date, recruitment is behind schedule, and no preliminary data are available (Alex Gottschalk, personal communication, April 2003).

OUTCOME OF PULMONARY EMBOLISM (PE)

In a European outcome study, the 1-year mortality (from all causes) in patients with PE was 18%, which was not significantly different from those in whom PE was excluded.[120] Of the patients with PE or DVT who are treated, the prevalence of death from recurrent disease is low. In a meta-analysis of 25 studies, including 5,523 patients, the rate of fatal PE during anticoagulant therapy was 0.4% in patients presenting with DVT and 1.5% in those presenting with PE.[15] The prevalence of death from either acute or recurrent PE within 1 year in patients who had a low pulmonary clot burden and were not anticoagulated was 5%.[121]

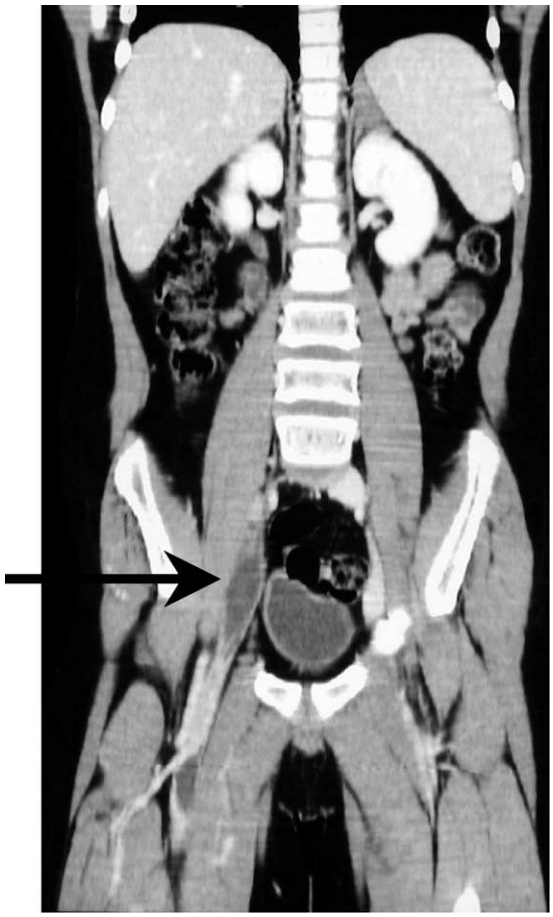

Fig 12. Coronal CT venography image showing a filling defect within the right iliac vein caused by a deep vein thrombosis.

Of the 399 patients in the PIOPED study who had confirmed PE, treatment was initiated for 94% (375 of 399). Of the 24 patients who were not treated, 19 had negative angiogram interpretations at the local hospital that were in disagreement with the final angiogram interpretation. Death attributed to PE occurred in only 2.5% (10 of 399) of patients with PE.[122] In the PIOPED study, patients suspected of having PE were far more likely to die of comorbid conditions rather than PE. Of the patients who died of PE, only one was untreated, and 9 of the deaths were caused by clinically suspected recurrent PE. Therefore, when properly diagnosed and treated, death attributed to PE was relatively uncommon.

Of the women who have PE, the presence of congestive heart failure, hypotension, or a coexisting malignancy was the clinical parameter that was associated with death.[22] Of men with PE, the presence of hypotension, tachypnea, coexisting malignancy, or increasing age was the best predictor of death.[22]

CONCLUSIONS

From the prospective and outcome based studies that have been performed in the last few years, the following conclusions regarding the radionuclide imaging in the evaluation of patients with suspected PE can be made:

1. A normal V/Q scan interpretation excludes the diagnosis of clinically significant PE.

2. Patients with very low or low probability V/Q scan interpretation and a low clinical likelihood of PE have a low (ie, less than 5%) prevalence of PE, and generally do not require angiography or anticoagulation.

3. Patients with very low or low probability V/Q scan interpretation, an intermediate to high clinical likelihood of PE, and negative, serial noninvasive venous studies of the lower extremities generally do not require anticoagulation. In selected cases, CT angiography would likely be helpful in excluding the diagnosis and providing an alternative diagnosis.

4. Clinically stable patients with an intermediate probability V/Q scan interpretation require noninvasive venous studies of the legs and, if negative, require CT angiography for a definite diagnosis.

5. Clinically stable patients with a high probability V/Q scan interpretation and a concordant clinical likelihood of PE, or those suspected of having a false-positive V/Q scan interpretation require treatment and need no further diagnostic tests to confirm the diagnosis.

6. Clinically stable patients with a high probability V/Q scan interpretation and a low clinical likelihood of PE require noninvasive venous studies of the legs and, if negative, often require CT angiography or pulmonary CT for a definitive diagnosis.

Proponents suggest that CT angiography should be used as the first line imaging test in patients with suspected PE. Others suggest that V/Q scanning should remain as the first line diagnostic imaging test and that CT angiography should be used in patient's in whom the diagnosis remains uncertain.[53,100,104,123] In patients with a normal chest radiograph, the V/Q lung scan is an effective, noninvasive initial study for evaluating those with suspected PE. CT angiography is more likely to provide a definitive diagnosis of PE or an alternative diagnosis in patients with significant chest radiographic abnormalities. Other factors influencing the choice of diagnostic tests are the clinical status of the patient, cost, availability, and expertise. The combination of CT angiography and CT venography has the potential to provide a single, comprehensive evaluation of patients with suspected venous thromboembolism.

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