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Advances in diagnosing and excluding pulmonary embolism: Spiral CT and D-dimer measurement

■ ABSTRACT

No single imaging study or blood test is 100% sensitive and specific for pulmonary embolism. A combination of pretest clinical probability assessment, noninvasive pulmonary imaging (V/Q scanning or spiral CT), and D-dimer testing seems prudent before pursuing pulmonary angiography.

■ KEY POINTS

In the PIOPED study, patients with a normal chest radiograph on presentation had a 13% likelihood of having an indeterminate V/Q scan, rising to 43% if the chest radiograph was abnormal. Therefore, it may be preferable to use spiral CT in patients with abnormal chest radiographs.

In patients with indeterminate V/Q and spiral CT scans or normal spiral CT scans, lower-extremity compression ultrasonography and D-dimer testing are advised. Absence of deep venous thrombosis and presence of a normal D-dimer level in these settings essentially rules out clinically significant pulmonary embolism. In patients with a high pretest clinical suspicion of pulmonary embolism, further imaging may be necessary, including pulmonary angiography.

Spiral CT continues to be studied as a substitute for pulmonary angiography.

WHAT IS THE BEST WAY to diagnose pulmonary embolism (PE)? That depends on the pretest probability that the patient has a PE and on other factors.

We now have two relatively new tests—helical (spiral) computed tomography (CT) and several blood tests for D-dimer—in addition to ventilation-perfusion lung scintigraphy (V/Q scanning) and pulmonary angiography. Each test has specific limitations and advantages; therefore, it seems prudent to individualize the approach to diagnosing PE on the basis of the patient's clinical presentation, comorbidities, and chest radiograph, and on whether imaging and interpretive expertise are available.

This article specifically discusses the use of spiral CT and D-dimer assays in the diagnosis and exclusion of pulmonary embolism.

■ COMMON AND SERIOUS

PE is a major cause of morbidity and mortality in the United States. A recent population-based study reported an annual incidence of 69 cases per 100,000 persons.¹

In treated patients with PE, all-cause mortality rates have been reported to be as high as 11% at 2 weeks and 17% at 3 months.² In untreated patients, death from PE occurs most frequently within 24 to 48 hours of initial presentation. In autopsy-based studies, PE has been identified as the proximate cause or contributor to death in 15% to 30% of all patients.³ Antemortem diagnosis may actually be made in fewer than one third of patients with suspected PE.³

When one includes confirmed and undiagnosed cases of PE, an estimate of 600,000 events per year in the United States seems reasonable.²

Failure to diagnose PE accurately and promptly can result in excess morbidity and death due to pulmonary hypertension and recurrent venous thromboembolic events. Conversely, unnecessary anticoagulation therapy poses a risk without any benefit. Therefore, it is imperative that PE be properly and quickly diagnosed or excluded to ensure optimal patient clinical outcome.

■ SIGNS AND SYMPTOMS ARE NONSPECIFIC

The signs and symptoms of PE are nonspecific and include:

- Chest pain (70% of patients)
- Tachypnea (70%)
- Cough (40%)
- Tachycardia (33%)
- Shortness of breath (25%)
- Signs of deep venous thrombosis (DVT; 10%)
- Syncope (5%).

Therefore, diagnosing PE on purely clinical grounds is challenging—and discouraged.^{2,4} The sensitivity and specificity of arterial blood gas abnormalities, chest radiographic abnormalities, and electrocardiographic abnormalities are low when considered alone. In fact, by itself, a high clinical suspicion accurately predicts PE in only 68% of cases.⁵

■ PULMONARY ANGIOGRAPHY: THE GOLD STANDARD

Pulmonary angiography is the historical gold standard for diagnosing PE, with which all other imaging tests have been compared.

Technique

Pulmonary angiography is performed via central venous access, most commonly the femoral vein. A catheter is passed through the venous system, through the right side of the heart, and into the main pulmonary arteries. Contrast is injected, and radiographic images of the pulmonary arterial tree are obtained.

PE is diagnosed if an intraluminal filling defect or arterial cutoff is seen in two imaging planes (perpendicular views).

Sensitivity and specificity

From three studies of clinical outcome, the sensitivity of pulmonary angiography was calculated to be 98% and the specificity 97%.⁶ Interinterpreter variability can be high, however, and the sensitivity of angiography for detecting peripheral, subsegmental PE has been questioned. Expert interpreters disagree more often on the absence of PE (17%) than on its presence (8%).⁵

Advantages and disadvantages

An advantage of angiography is that one can perform adjunctive procedures such as suction thrombectomy, local catheter-directed thrombolysis, and placement of an inferior vena cava filter at the same time as the diagnostic procedure.

Furthermore, unlike V/Q scanning, pulmonary angiography can be used to differentiate between acute and chronic PE (in which pruning of vessels and calcified mural irregularities can be seen).

Disadvantages of pulmonary angiography are that it is invasive and associated with death in 0.5% of cases, major complications in 1%, and minor complications in 5%.⁷

Comments. Pulmonary angiography is most often used as a second-line diagnostic test, especially in patients with an indeterminate V/Q scan.

■ V/Q SCANNING: THE MOST POPULAR TEST

V/Q scanning is the most frequently ordered diagnostic test in patients with clinically suspected PE.

Technique

V/Q scanning consists of two studies: perfusion (Q) and ventilation (V) scintigraphy.

Perfusion scintigraphy (Q scanning) is performed using an intravenous injection of macroaggregated particles of technetium 99m-labeled human serum albumin. The particles are the same size as the pulmonary capillaries and become trapped in approximately 0.1% of

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**TABLE 1**

The PIOPED study: Likelihood of angiographic diagnosis of PE, by V/Q scan results and pretest clinical probability

V/Q SCAN RESULT	CLINICAL PROBABILITY		
	HIGH	INTERMEDIATE	LOW
High-probability	28/29 (96%)	70/80 (88%)	5/9 (56%)
Intermediate-probability	27/41 (66%)	66/236 (28%)	11/68 (16%)
Low-probability	6/15 (40%)	30/191 (16%)	4/90 (4%)
Near-normal or normal	0/5 (0%)	4/62 (6%)	1/61 (2%)
Total	61/90 (68%)	170/569 (30%)	21/228 (9%)

ADAPTED FROM 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.

them. On gamma camera images, any obstruction to arterial flow appears as an area of non-perfusion or underperfusion, termed a “perfusion defect.”

Because diseases that narrow airways (eg, asthma and emphysema) or fill alveoli with fluid (eg, pneumonia and heart failure) can precipitate hypoxic pulmonary vasoconstriction, pulmonary hypoperfusion is not specific for PE. The presence of segmental or multiple segmental perfusion defects increases the specificity for PE.

Ventilation scintigraphy (V scanning) in patients with abnormal Q scans helps improve the specificity of the test.

V scanning involves inhalation of a radioactive gas (xenon 133 or krypton 81m) or aerosolized technetium-99m, which provides an image of all ventilated portions of the lung.

On the basis of the presence and extent of matched defects (absence of both perfusion and ventilation) and unmatched defects (absence of perfusion with preserved ventilation), the V/Q scan can be interpreted using published criteria as either being normal or showing a low, intermediate, or high probability of PE.^{5,8,9}

Interpreting V/Q scanning results

The Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study addressed the diagnostic utility of V/Q scan-

ning in patients with suspected acute PE.^{5,8,9} The diagnostic accuracy of V/Q scanning alone and V/Q scanning combined with an empiric assessment of clinical probability (low, intermediate, or high clinical suspicion) were compared with the results of pulmonary angiography. Findings:

- A normal or near-normal V/Q scan by itself has a high negative predictive value, essentially excluding PE (< 5% probability).
- A high-probability V/Q scan by itself has a high positive predictive value (approximately 90%), which has led most physicians to consider such a scan as diagnostic of PE.
- The positive predictive value of a high-probability scan in the setting of a low pretest clinical suspicion was only 56%, but this combination is found in very few patients.
- A nondiagnostic (indeterminate) V/Q scan, ie, one that is interpreted as low-probability or intermediate-probability, neither confirms nor refutes the diagnosis of PE and is best interpreted in the context of clinical suspicion and additional testing (TABLE 1).^{5,8,9} For example, PE is unlikely in patients in whom there is a low clinical suspicion for PE and a low-probability V/Q scan.

Assessment of pretest clinical probability can be empiric (gut instinct based on signs and symptoms)^{5,10} or based on published prediction rules.^{11,12}

Both means of assessing the clinical likelihood of PE are effective at stratifying

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TABLE 2

Performance characteristics of spiral CT for detecting pulmonary embolism

AUTHOR	YEAR	NO. OF PATIENTS	LEVEL OF ANALYSIS	SENSITIVITY (%)	SPECIFICITY (%)
Goodman ²¹	1995	20	Central vessels (lobar and segmental)	86	92
			Central and subsegmental	63	89
Rémy-Jardin ¹⁴	1992	42	Central	100	90
Garg ²²	1998	24	Central	100	100
			Central and subsegmental	67	100
Drucker ¹⁶	1998	47	Central	53	97
Kim ¹⁷	1999	110	Central	92	96
Mayo ¹⁸	1997	142	Central	87	95
van Rossum ¹⁹	1996	149	Central	94	96
Rémy-Jardin ²⁰	1996	75	Central	91	78
Grenier ¹⁵	1998	139	Central	87	95

Many V/Q scans are nondiagnostic: 73% in the PIOPED study

patients into low, intermediate, and high clinical probability groups. The scoring system of Wicki et al¹² is standardized but requires arterial blood gas sampling. The scoring system of Wells et al¹¹ requires operator judgment on the probability of an alternative (non-PE) diagnosis. We rely on our empiric assessment.

Other combinations of clinical probability and V/Q scanning results usually call for additional testing before a diagnosis can be made. Patients with suspected PE in whom treatment is withheld on the basis of a low pretest clinical probability and a nondiagnostic V/Q scan have been shown to have a very low (1.7%) 3-month thromboembolic risk as long as lower-extremity compression ultrasonography did not reveal proximal DVT.¹⁰

Advantages, disadvantages of V/Q scanning: Noninvasive, but often nondiagnostic

V/Q scanning is noninvasive and entails only a limited exposure to radiation. In addition, it is widely available and most radiologists have had extensive experience with it.

On the other hand, V/Q scanning produces many nondiagnostic studies: 73% in the PIOPED study,⁵ and as many as 90% in patients with underlying chronic obstructive pulmonary disease or other underlying pulmonary processes that can result in an

abnormal chest radiograph.¹³ The high prevalence of nondiagnostic studies and the failure of many physicians to establish a clinical probability for the likelihood of PE before obtaining and interpreting a V/Q scan are significant limitations to its use as a diagnostic tool.

Moreover, V/Q scanning cannot determine the acuity of PE. In patients with suspected recurrent PE, a single V/Q scan cannot differentiate between acute or chronic disease. If prior scans are available for comparison, one can merely identify new defects (mismatches) as they appear.

Comments. A V/Q scan is an appropriate first test to evaluate a patient with suspected PE. However, if the baseline chest radiograph is abnormal, or if there is a history of significant underlying pulmonary disease or a past history of PE, a V/Q scan may not provide the necessary information to diagnose or exclude acute PE.

■ HELICAL (SPIRAL) COMPUTED TOMOGRAPHY

Since 1992, when Rémy-Jardin and colleagues¹⁴ published their series on spiral CT, interest in its use as a diagnostic test for PE has mounted.

**TABLE 3****Comparison of the three main imaging tests used to diagnose pulmonary embolism**

	V/Q SCAN	SPIRAL CT	PULMONARY ANGIOGRAPHY
Sensitivity	98%	53%–100%	98%
Specificity	10%	78%–100%	97%
Interobserver agreement	0.61	0.77–0.85	0.81
Nondiagnostic scans	73%	2%–9%	3%
Advantages	Noninvasive Widely available Extensive experience Very sensitive for PE	Noninvasive Helps achieve an alternative diagnosis Good interobserver agreement Can differentiate acute from chronic PE	Gold-standard test Facilitates intervention Can differentiate acute from chronic PE
Disadvantages	2/3 of scans are nondiagnostic Poor interobserver agreement Cannot differentiate acute from chronic PE	Requires IV contrast Misses subsegmental PE	Invasive Requires IV contrast

In view of the merits of spiral CT, some investigators have suggested that it should replace V/Q scanning as the initial test of choice for diagnosing PE. Others advocate that it be used as the confirmatory test of choice in place of pulmonary angiography. Still others feel that additional comparative data are needed before widespread use of spiral CT is warranted (TABLE 2).

Technique

Spiral CT uses “slip-ring” technology that allows continuous CT scanning and dynamic contrast injection. A study can be completed in less than 30 seconds and in a single breath-hold. This virtually eliminates motion artifact and allows evaluation of moving structures such as the lungs and blood vessels.

Contrast is injected during scanning in a continuous bolus via a peripheral vein. This allows visualization of the heart and pulmonary arterial bed. The data are obtained as a “volume” rather than as individual slices and can be reconstructed at overlapping intervals to improve image resolution.

PE is diagnosed by identifying a filling defect in the pulmonary arteries, such as com-

plete occlusion of the vessel, mural defects along the vessel wall, or tracking of contrast around central thrombus.¹⁵ Ancillary signs such as pleural effusion or pulmonary infarct may also be identified.¹⁵

Sensitivity and specificity

Compared with V/Q scintigraphy or pulmonary angiography, the sensitivity of spiral CT has ranged from 53% to 100% and its specificity from 78% to 100% (TABLE 3).^{14–22} These wide variations in performance characteristics may in part be explained by variations in image-acquisition protocols among studies.

Spiral CT is less sensitive for subsegmental defects

Spiral CT is best used to identify thrombus within the main pulmonary artery, lobar pulmonary arteries, and first-order segmental branches of the pulmonary artery. Goodman and colleagues²¹ demonstrated that the sensitivity of spiral CT shifted from 86% when only central vessels were imaged to 63% when the subsegmental vessels were included. When considering only segmental PE, Garg et al²² documented a sensitivity of 100%; how-

Up to 67% of spiral CT scans can lead to or support an alternative diagnosis

ever, when subsegmental vessels were evaluated, the sensitivity decreased to 67%.

Whether subsegmental PE is clinically significant and needs to be definitively detected has been debated and is a central issue to consider when choosing a diagnostic test. Data from PIOPED suggest that only 6% of PEs are subsegmental.⁵ The effects of a subsegmental PE may be negligible in patients with normal cardiopulmonary function. However, a subsegmental PE could be disastrous in a patient with decreased cardiopulmonary reserve or severe underlying lung disease.

There is also always the danger of fatal recurrent PE in patients with an initial subsegmental event. In a series of patients with low-probability lung scans and diminished cardiopulmonary reserve, 6 (7.8%) of 77 died of autopsy-confirmed PE, compared with 1 (0.14%) of 711 patients with good cardiopulmonary reserve ($P < .0001$).²³

Two recent meta-analyses that evaluated spiral CT in the diagnosis of PE suggested that there was currently insufficient evidence to rely on a negative spiral CT scan to justify withholding anticoagulation or to support the insignificance of undetected subsegmental PE.^{24,25}

However, two additional studies followed the outcomes of patients in whom anticoagulation was withheld following a negative spiral CT:

- Ferretti et al²⁶ prospectively followed 109 patients who had indeterminate V/Q scans, negative duplex ultrasonogram of the lower extremities, and negative spiral CT scans. In 3 months of follow-up, 1 patient died of clinically suspected PE, and 2 others developed clinical symptoms of PE that were confirmed by V/Q scanning.
- Lomis et al²⁷ retrospectively studied the outcome of 100 patients following negative spiral CT arteriography. No patient developed confirmed PE during 6 months of follow-up.

Advantages and disadvantages of spiral CT

One benefit of spiral CT is that up to 67% of scans can lead to or support an alternative diagnosis to explain a patient's presenting symptoms.^{17,19} Therefore, spiral CT may be the optimal initial test for patients with an abnormal baseline chest radiograph. Unlike

V/Q scanning, spiral CT can be effectively used to differentiate between acute and chronic PE.²⁸⁻³⁰

On the other hand, spiral CT has both clinical and technical limitations. It requires intravenous contrast, making it undesirable in patients with a history of contrast allergy or underlying renal insufficiency. It also requires patient cooperation: patients must hold their breath for 10 to 30 seconds, which could be difficult for those with dyspnea or altered mental status.

Interpretive pitfalls in spiral CT

In addition, numerous technical considerations and pitfalls can lead to false interpretation.³¹ Factors that may influence the ability to interpret a scan due to inadequate contrast in the pulmonary vasculature include patient respiration, improper scan delay (the time between injection of contrast and acquisition of images), and superior vena cava obstruction.

In patients unable to cooperate with breath-holding, breathing artifacts can change the orientation and the diameter of vessels. In addition, the pulmonary arterial flow rate changes with the phase of respiration and may result in variable arterial opacification.

The proper scan delay is important for proper vessel opacification. If the scan delay is too short, there is not enough time to allow opacification of the pulmonary arteries on the first images, thus resulting in "pseudofilling" defects. If the scan delay is too long, there is not enough contrast material left at the end of the study.

Obstruction of the superior or inferior vena cava can cause delayed and suboptimal opacification of the pulmonary arteries. Hilar lymphadenopathy or other mediastinal soft-tissue masses can mimic the appearance of PE.

Any shunt can make the CT scan more difficult to interpret, whether due to a patent foramen ovale, intrapulmonary circulation from pleuroparenchymal disease, or a left-to-right cardiac shunt with prominent bronchopulmonary circulation.³¹

Comments. Whether spiral CT is better than, worse than, or equivalent to pulmonary angiography in detecting clinically relevant PE remains to be determined. A normal spiral

Whether spiral CT is better than pulmonary angiography remains to be determined



CT scan does not rule out PE, and like V/Q scanning, spiral CT should be combined with an assessment of clinical probability and other diagnostic tests to arrive at a diagnosis.

In the PIOPED study, patients with a normal chest radiograph on presentation had a 13% likelihood of having an indeterminate V/Q scan, rising to 43% if the chest radiograph was abnormal. Therefore, it may be preferable to use spiral CT in patients with abnormal chest radiographs.

■ D-DIMER MEASUREMENTS

Monoclonal antibodies specific for the cross-linked fibrin region known as D-dimer have been developed and shown to be sensitive for detecting increased plasma concentrations of cross-linked fibrin degradation products.

D-dimer is generated by plasmin-mediated proteolysis of fibrin that has been cross-linked by thrombin-activated coagulation factor XIII. Increased plasma concentrations of D-dimer reflect thrombus formation and concomitant activation of the fibrinolytic cascade.

Because D-dimer is derived from lysed thrombus and not from circulating fibrinogen, D-dimer assays have been extensively studied as tests for venous thromboembolism. These assays differ in their ease of use, turnaround time, cost, and sensitivity and specificity for PE.

Types of D-dimer assays

ELISAs. Traditional quantitative enzyme-linked immunosorbent assays (ELISAs) are labor-intensive, costly, time-consuming, and best reserved for batch testing.

Traditional D-dimer ELISAs performed using conventional 96-well microtiter plates have been shown to be highly sensitive for acute PE at a cutoff value of 500 ng/mL.³² For detecting PE, the sensitivity has been reported as 93% to 100%, specificity 25% to 50%, and negative predictive value 91% to 100%. Thus, a D-dimer level below 500 ng/mL reasonably rules out acute PE as well as acute DVT.

Newer, rapid ELISA-derived assays can generate single patient results in 10 to 35 minutes without sacrificing sensitivity and negative predictive value for PE.³²

Traditional qualitative latex agglutination assays are relatively inexpensive, widely available, and rapid, but lack the desired level of sensitivity and negative predictive value for acute PE.³² Latex agglutination assays have demonstrated a sensitivity range of 84% to 96%, a specificity of 21% to 56%, and a negative predictive value of 83% to 93%.³²

A semiquantitative whole-blood hemagglutination assay (WBA) called SimpliRED (AGEN, Brisbane, Australia) can be performed at a patient's bedside in about 2 minutes with a sensitivity range of 84% to 94%, a specificity of 66% to 68%, and a negative predictive value of at least 96% for PE.³² A very recent study of emergency department patients presenting with suspected venous thromboembolic events, however, questioned the use of WBA for excluding PE.³³

How should D-dimer testing be used?

How best to use D-dimer testing in the setting of acute venous thromboembolism, including PE, remains to be determined. Some centers use D-dimer testing as a standalone PE screening test: if the value is not elevated, there is no need for any radiographic imaging test. Other centers reserve D-dimer testing for patients with a nondiagnostic V/Q scan, nondiagnostic spiral CT scan, or normal spiral CT scan prior to pursuing more invasive testing.^{34–37} No study has compared these D-dimer test approaches to determine which is more practical, cost-effective, or accurate.

D-dimer testing is nonspecific, and not sensitive in some groups

D-dimer testing is not only nonspecific but also lacks acceptable sensitivity in certain settings and patient subgroups. It has a documented false-negative rate between 9% and 15% when performed in patients with symptoms suggesting venous thromboembolism.^{34–36,38,39} In a recent study of patients with documented venous thromboembolic events, 26 (22%) of 119 had a false-negative D-dimer test.⁴⁰

Small localized thrombi and thrombi more than 2 weeks old may not generate sufficient D-dimer and may result in false-negative D-dimer assay results.^{38,41}

Many conditions can cause elevated D-dimer levels

The specificity of D-dimer testing is particularly low in the very elderly suspected of having PE (9% in patients older than 80 years).⁴² In cancer patients, who are at high risk for venous thromboembolism because of the hypercoagulability of malignancy, D-dimer testing may lack sensitivity, specificity, and adequate negative predictive value in excluding PE.³⁷ Therefore, D-dimer testing is best reserved for otherwise healthy outpatients suspected of having acute PE.

In addition, many conditions can lead to an elevation in D-dimer, including venous thromboembolism, myocardial infarction,

pneumonia, sepsis, disseminated intravascular coagulation, liver disease, malignancy, surgery, hemorrhage, and trauma. Thus, D-dimer testing may be specific for cross-linked fibrin degradation products, but cross-linked fibrin degradation products are not specific for PE. However, the ELISA and WBA tests have sufficiently high sensitivity and negative predictive values to be useful in excluding the diagnosis of venous thromboembolism.

Comments. A positive D-dimer assay is of limited diagnostic utility, but a negative test essentially excludes venous thromboembolism.

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