

New Approaches to the Diagnosis of Pulmonary Embolism

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Pulmonary embolism (PE) is recognized as the third most common cause of cardiovascular disease in the United States after ischemic heart disease and stroke.¹ Autopsy studies suggest that more than 600,000 patients in the United States develop PE each year and that this entity causes or contributes to death in approximately 200,000 of these patients.² Because treatment can reduce the mortality rate of PE from 30% to less than 10%, prompt and accurate diagnosis of both PE and its precursor, deep venous thrombosis (DVT), is essential.² Unfortunately, the clinical symptoms and signs of both of these disorders are nonspecific. The presence of one or more risk factors for DVT, including immobility, injury to an extremity, or hypercoagulability, is a clue to the possibility of DVT or PE. The ventilation-perfusion (V/Q) scan has traditionally been the pivotal diagnostic test for PE, but most V/Q scans are nondiagnostic and further testing is usually required.³ Although pulmonary angiography is considered the gold standard for the diagnosis of PE, angiography is invasive, expensive, and not available at all hospitals.⁴ Therefore, interest has focused on the development of new noninvasive approaches for the diagnosis of PE. Recently, technologic advances have allowed the use of spiral (helical) computed tomography (CT) and magnetic resonance imaging (MRI) for the diagnosis of PE. In addition, interest has been renewed in the use of echocardiography and the D-dimer test for the diagnosis of PE. This review summarizes recent data on these noninvasive techniques and describes their current role in the evaluation of patients with suspected PE. The key points of this article are summarized in the **Sidebar**.



CLINICAL EVALUATION OF PULMONARY EMBOLISM

Patient history, physical examination findings, and the results of arterial blood gas studies, electrocardiography, and chest radiography are often useful for suggesting the presence or absence of PE. Clinical findings alone, however, are not a reliable guide to the diagnosis of PE, as is underscored by the high incidence of unsuspected PE in autopsy series.⁵ The presence

of risk factors for DVT may lower the threshold for initiating diagnostic evaluation for PE. Common risk factors for DVT are listed in **Table 1**. The presence of one or more risk factors should increase clinical suspicion of venous thromboembolism (VTE).

PE should be considered whenever unexplained dyspnea occurs. Dyspnea with or without associated anxiety, pleuritic chest pain, and hemoptysis are common but nonspecific symptoms of PE. Any of these symptoms may also develop with several other conditions such as pneumonia, exacerbated chronic obstructive lung disease, congestive heart failure, or lung cancer. Lightheadedness and syncope may be caused by PE but may also result from several other entities that cause hypoxemia or hypotension.

Physical examination of a patient with PE may reveal tachypnea, tachycardia, fever, and pleuritic rub, all of which are nonspecific symptoms. Tachypnea and tachycardia are extremely common findings. Findings consistent with pulmonary hypertension caused by acute PE

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KEY POINTS IN THE DIAGNOSIS OF PULMONARY EMBOLISM

- Clinical suspicion for acute pulmonary embolism (PE) is absolutely critical.
- Currently, ventilation-perfusion (V/Q) scanning remains the most widely available and best-studied technique for the evaluation of patients with PE. When technically adequate, a negative result on lung perfusion scanning reliably excludes acute PE. In the setting of a high clinical suspicion for PE, a high-probability V/Q scan is considered diagnostic, and no further testing is indicated.
- Most V/Q scans are nondiagnostic and many patients require further testing to rule in or rule out PE. Pulmonary angiography is invasive, expensive, and carries certain small risks of morbidity and mortality; however, this technique remains the gold standard for diagnosing PE.
- Recent technological advances have made spiral computed tomography (CT) and magnetic resonance imaging (MRI) potentially useful diagnostic modalities for the evaluation of patients with suspected PE. Current data suggest that the sensitivity and specificity of spiral CT is high enough that this modality may eventually replace the V/Q scan as the initial diagnostic test, although additional outcome studies are needed. Currently, spiral CT is a viable option for the evaluation of suspected PE at certain centers that have expertise and experience with this technique.
- As technology continues to improve, MRI, with its potential ability to simultaneously diagnose both deep venous thrombosis and PE, may evolve into the procedure of choice for select patients with suspected PE.
- Hematologic studies such as the D-dimer test, although not currently playing a significant role in the diagnosis and treatment of venous thromboembolism at most centers, may evolve into more useful techniques, particularly as rapid assays become more widely available and when these studies are used together with other noninvasive diagnostic modalities.
- Lower extremity studies are often useful when the V/Q scan is nondiagnostic and the patient is hemodynamically stable. The leg studies are most useful when results are positive for deep venous thrombosis because the treatment approach is generally the same.

Table 1. Common Risk Factors for Deep Venous Thrombosis

Risk Factor	Hypercoagulable State
Age > 40 years	Antithrombin III deficiency
Recent surgery	Protein C or S deficiency
Malignancy	Factor V Leiden mutation
Pregnancy or postpartum	Antiphospholipid antibody syndrome
Immobilization or paralysis	Dysfibrinogenemia
Prior history of venous thromboembolism	Plasminogen disorders

include an accentuated pulmonic component of the second heart sound, right ventricular heave, and elevated neck veins. These symptoms occur more often in massive PE or in cases in which chronic emboli have caused severe pulmonary hypertension. In the setting of findings consistent with PE, clinical suspicion for PE is essential.

Hypoxemia is common in acute PE, but is not universally present. Young patients without underlying lung disease may have a normal partial pressure of oxygen in arterial blood (PaO₂). In a retrospective analysis of hospitalized patients with proven PE, PaO₂ was greater than 80 mm Hg in 29% of patients younger than age 40 years compared with 3% of patients older than age 40 years; however, the alveolar-arterial difference was abnormal in all patients.⁶ Even the alveolar-arterial difference may be normal in rare cases of PE, particularly in younger patients without concomitant lung disease.

Nonspecific electrocardiographic abnormalities may develop in acute PE, including T-wave changes, ST segment abnormalities, and left or right axis deviation. Occasionally, electrocardiographic changes that are more suggestive of PE occur, including the S₁Q₃T₃ pattern, right bundle branch block, P-wave pulmonale, or right axis deviation.⁷

Chest radiographs of most patients with PE show nonspecific abnormalities. Common radiographic findings include atelectasis, pleural effusion, pulmonary infiltrates, and elevation of a hemidiaphragm.⁸ Classic radiographic findings of pulmonary infarction, such as a wedge-shaped pleural density (Hampton's hump) or decreased vascularity (Westermark's sign), are suggestive of PE but are infrequent. A normal-appearing chest radiograph in a patient with severe dyspnea and hypoxemia without evidence of bronchospasm or cardiac shunt strongly suggests PE. The presence of a pleural effusion

Table 2. Probability of Pulmonary Embolism Based on Ventilation-Perfusion Scan Results and Level of Clinical Suspicion in the PIOPED Study

Ventilation-Perfusion Scan Results	Patients with PE, %		
	Level of Clinical Suspicion		
	Highly Likely	Uncertain	Unlikely
High probability	96	88	56
Intermediate probability	66	28	16
Low probability	40	16	4
Near-normal or normal	0	6	2

PE = pulmonary embolism; PIOPED = Prospective Investigation of Pulmonary Embolism Diagnosis.

Data from Value of the ventilation/perfusion scan in acute pulmonary embolism: results of the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED). The PIOPED Investigators. *JAMA* 1990;263:2753-2759.

increases the likelihood of PE in young patients who present with acute pleuritic chest pain.⁹ Generally, chest radiography cannot be used to conclusively prove or exclude PE; however, this modality and electrocardiography may be useful for determining alternative diagnoses.

VENTILATION-PERFUSION SCAN

The V/Q scan is considered the pivotal test for diagnosing PE. When PE is suspected, this test is commonly performed. The Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study, a large prospective multicenter trial, was undertaken to assess the diagnostic use of the V/Q scan.³ Results of scans were correlated with pulmonary angiography results in more than 700 patients. The PIOPED study provided important information regarding the utility of the V/Q scan and demonstrated that the likelihood of PE depends on the combination of clinical assessment and V/Q results. The PIOPED study results are summarized in **Table 2**. In the setting of low clinical suspicion and near-normal or normal V/Q scan results, only one of 61 patients (1.6%) had PE. In the setting of high clinical suspicion and a high probability scan, 28 of 29 patients (96%) had PE. Therefore, in these settings, V/Q scans are able to determine the likelihood of PE with sufficient certainty that no further tests are needed. Unfortunately, the V/Q scan is rarely diagnostic (ie, the scan is rarely interpreted as near normal or normal or as high probability). In the PIOPED study, only 13% of patients (124 of 931) had high probability scans and only 14% of patients (131 of 931) had normal or near-normal scans. Therefore, most scans in the PIOPED study were intermediate or low probability. The PIOPED study data demonstrate that PE is often present in patients with intermediate

or low probability lung scans when associated with a high clinical suspicion of PE. As shown in Table 2, in the setting of high clinical suspicion, PE was found in 66% of patients with an intermediate-probability scan and 40% of patients with low-probability scans. Therefore, additional diagnostic tests must be pursued when the V/Q scan is of low or intermediate probability if the clinical scenario suggests PE. In most patients who need additional diagnostic testing, pulmonary angiography is performed; however, in select stable patients with suspected acute PE and nondiagnostic lung scans, serial, noninvasive, lower extremity testing is a reasonable alternative approach. When DVT is present, treatment can generally be instituted without further testing.¹⁰ In many cases, however, the results of the lower extremity test are negative and a reassessment of clinical suspicion should be undertaken with consideration of pulmonary angiography to provide a definitive diagnosis.

PULMONARY ANGIOGRAPHY

Pulmonary angiography remains the gold standard for the diagnosis of PE. This test is most commonly employed in patients with nondiagnostic V/Q scans and high clinical suspicion. Angiography is not without risk, however, and serious morbidity and mortality occur in approximately 1% and 0.5% of cases, respectively. In the PIOPED study, death occurred in five of 1111 patients (0.5%) in whom pulmonary angiography was performed.⁴ Other serious complications associated with pulmonary angiography included respiratory failure (0.4%), renal failure (0.3%), and bleeding requiring more than 2 units of transfused blood (0.2%).⁴ In addition, although pulmonary angiography is considered the gold standard for the diagnosis of PE, interobserver agreement on the presence of PE in the

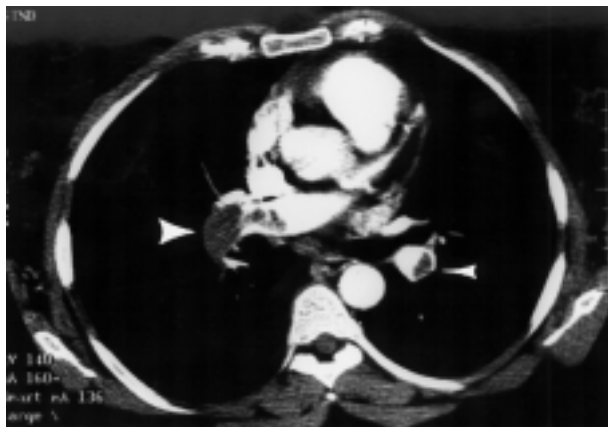


Figure 1. Spiral computed tomography scan of the chest after bolus contrast injection. A large clot in the right pulmonary artery is shown (*large white arrow*). A smaller clot is also apparent in the left pulmonary artery (*small white arrow*).

PIOPED study was 92%, which suggests that even angiogram results can be difficult to interpret in some cases.³ Therefore, although angiography is considered the most accurate diagnostic modality for PE, this test is invasive, has small but significant risks, and requires experienced physicians to perform the test and interpret the results.

SPIRAL (HELICAL) COMPUTED TOMOGRAPHY

Recent advances in CT technology have led to the investigation of spiral CT for the diagnosis of acute PE. Conventional CT is generally not useful in the evaluation of PE because the long time required for scanning and the interscan delay limit the ability to adequately enhance and visualize pulmonary arteries. Spiral CT involves continuous movement of the patient through the CT scanner with concurrent scanning by a constantly rotating gantry and detector system, which facilitates rapid scanning times and allows volumes of data to be obtained during a single breath hold. Continuous scanning during a breath hold after contrast injection allows excellent visualization of the pulmonary arteries and direct visualization of pulmonary arterial clot in larger vessels. Spiral CT is an attractive alternative approach to evaluate suspected PE. A primary advantage of this technique is the ability to visualize mediastinal and chest wall structures such as lymph nodes, lung parenchyma, pleurae, and pericardium. Consequently, abnormalities other than PE that are causing or contributing to a patient's symptoms may also be identified. **Figure 1** illustrates the identification of a proximal pulmonary artery clot by spiral CT in a patient with acute PE.

Comparison with Pulmonary Angiography

Several studies compared spiral CT with pulmonary angiography for the detection of acute PE (**Table 3**).¹¹⁻¹⁶ Based on available data, proximal pulmonary emboli can apparently be diagnosed with a fairly high degree of sensitivity and specificity with spiral CT; however, outcome data based on spiral CT results are limited. One study¹⁷ used spiral CT instead of pulmonary angiography in patients with suspected PE only after a V/Q scan of intermediate probability and normal results on duplex ultrasonography. If the CT scan did not show PE, the patient did not receive anticoagulation therapy. At 3-month follow-up, six of 112 patients (5.4%) with normal findings at spiral CT had PE (ie, the results of six CT scans were apparently false-negative). The rate of PE at follow-up in patients with negative pulmonary angiogram results was slightly lower, ranging from 0.6 to 4.2% in several studies.¹⁷ As spiral CT and image reconstruction technology continue to improve, the sensitivity and specificity of this technique for the diagnosis of PE should also improve.

Limitations

Spiral CT has several limitations as a method for diagnosing PE. First, although the initial data look encouraging, the actual number of patients with PE in each study is relatively small (**Table 3**). Because the sensitivity of spiral CT appears to be lower than that of angiography, additional larger prospective studies are needed to determine outcomes in patients with negative results on CT scans. Second, although spiral CT is very sensitive for detecting emboli in the main, lobar, or segmental pulmonary arteries, visualization of subsegmental arteries is limited. In one study, when subsegmental emboli were included with the central clot, the overall sensitivity of spiral CT was reduced from 86% to 63%;¹⁶ however, the importance of smaller, subsegmental pulmonary emboli is controversial, and isolated subsegmental emboli are uncommon, occurring in only 6% of patients in the PIOPED study.³ Additional studies are needed to determine if the inability of spiral CT to visualize subsegmental emboli is clinically important. Third, spiral CT scan requires interpretation by an experienced radiologist who has precise knowledge of bronchovascular and intersegmental lymph node anatomy. Nodal structures can obscure vessels and may be misinterpreted as emboli by inexperienced readers. Fourth and finally, the requirement for iodinated contrast may preclude the use of spiral CT in some patients who have a severe allergy to this contrast material or who have renal insufficiency. As has been demonstrated with nondiagnostic V/Q scanning, the performance of

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Table 3. Sensitivity and Specificity of Spiral Computed Tomography for Acute Pulmonary Embolism

Study	Patients Evaluated, n	Patients with PE, n	Sensitivity, %	Specificity, %
Remy-Jardin et al, 1992 ¹¹	42	18	100	96
Remy-Jardin et al, 1996 ¹²	72	39	91	78
van Rossum et al, 1996 ¹³	77	39	95	97
Sostman et al, 1996 ¹⁴	28	21	73	97
Goodman et al, 1995 ¹⁵	20	11	86	92
Mayo et al, 1997 ¹⁶	139	46	87	95

PE = pulmonary embolism.

serial lower extremity studies may prove appropriate when a spiral CT is nondiagnostic.

MAGNETIC RESONANCE IMAGING

Recent advances in imaging technology have made visualization of the pulmonary arteries possible with MRI, thus creating a potential diagnostic role for MRI in patients with clinically suspected PE.¹⁸ Like CT, MRI demonstrates PE directly as intravascular filling defects on cross-sectional images. Meaney et al¹⁹ recently prospectively compared gadolinium-enhanced magnetic resonance angiography with pulmonary angiography in 30 patients with suspected PE. The patients were enrolled consecutively, and the studies were interpreted independently in a blinded manner by three radiologists. Criteria for the diagnosis of PE for both tests were the presence of an intravascular filling defect or occlusion of a vessel with a trailing embolus sign. The pulmonary angiogram result was considered the definitive diagnosis. In eight patients with emboli proven by pulmonary angiography, all five lobar and 16 of 17 segmental emboli were identified by the MRI technique. The sensitivities for magnetic resonance angiography for each of the readers were 100%, 87% and 75%, with specificities of 95%, 100%, and 95%, respectively.

Advantages

Although experience with MRI in the diagnosis of acute PE is more limited than with CT, MRI has several theoretical advantages. First, MRI techniques can image both the pulmonary arteries and deep venous system and may allow the simultaneous and accurate detection of both PE and DVT. In patients with suspected PE, documentation of DVT generally provides enough information to initiate treatment. In addition, in patients with acute PE, the simultaneous identification of DVT may be useful to identify patients at higher risk of recurrent PE. Second, unlike spiral CT, MRI

does not require the use of iodinated contrast material and can be performed safely in patients with iodinated contrast allergy or renal insufficiency.

Limitations

Despite these potential advantages, MRI is clinically limited by the inability to image patients who are morbidly obese, claustrophobic, or have metallic implants. In addition, data on the use of MRI for the diagnosis of PE are still limited. The actual number of patients with suspected PE that have been evaluated with MRI and reported is relatively small and additional studies are needed. Moreover, a recent study compared MRI with spiral CT for the diagnosis of PE and determined that although MRI and CT had comparable sensitivity and specificity when read by experts, the sensitivity for MRI dropped dramatically with less experienced readers.¹⁴ These findings suggest that reader expertise is essential for the broader application of MRI techniques to PE. Although spiral CT is being used increasingly for suspected PE and MRI is being evaluated more extensively in this setting, additional, larger, prospective clinical studies should be performed. Outcome studies appear particularly appropriate. Certainly if any question remains about the diagnosis of PE based on spiral CT or MRI results, the traditional approach including angiography should be undertaken.

ECHOCARDIOGRAPHY

Transthoracic echocardiography can be rapidly obtained at most institutions, and thus this modality is an attractive diagnostic test. Studies of patients with documented PE reveal that most of these patients have abnormalities of right ventricular size or function as noted on surface echocardiography.²⁰ Unfortunately, although right ventricular dysfunction is suggestive of PE, this finding is nonspecific and certain clinical conditions commonly found in patients with suspected PE (eg, chronic

obstructive pulmonary disease) are also associated with abnormal right ventricular function, thus limiting the utility of echocardiography for the diagnosis of PE. A recent study suggests that the identification of regional right ventricular dysfunction enhances the specificity of surface echocardiography for acute PE,²¹ however, additional studies confirming this finding would be useful. Unfortunately, poor visualization of intrathoracic structures limits the utility of echocardiography in many patients with suspected PE, especially obese patients and patients with severe hyperinflation caused by chronic obstructive lung disease. Transesophageal echocardiography also has been used for the diagnosis of PE, but poor visualization of the peripheral pulmonary arteries limits the utility of this method for acute PE. Therefore, echocardiography does not yet have a clear role in the standard diagnostic approach to patients with suspected PE. Echocardiography may also be useful in detecting alternative diagnoses such as left ventricular dysfunction, pericardial effusion, or valvular heart disease.

D-DIMER ASSAY

Noninvasive blood tests have been evaluated in hopes of identifying a specific marker for VTE. D-dimer is a specific degradation product released into the circulation when cross-linked fibrin clots undergo endogenous fibrinolysis.²² Several clinical trials have been undertaken to determine the utility of this test in the diagnosis of VTE. Generally, either an enzyme-linked immunosorbent assay (ELISA) or a latex agglutination test is performed. Although an elevated D-dimer assay alone is too nonspecific to be diagnostic of DVT or PE, the quantitative ELISA appears to be quite sensitive. The latex agglutination studies, however, do not share the same sensitivity. Unfortunately, low D-dimer levels are found in only approximately 25% of patients without PE, a fact that limits the clinical utility of this test. Many other causes for elevation of D-dimer levels exist, including surgery, infection, and cancer. Furthermore, results of studies using one manufacturer's D-dimer assays cannot be extrapolated to another manufacturer's assays, and no single test has been established as superlative. Several very encouraging outcome studies have been performed that emphasize the utility of a negative D-dimer value for excluding DVT²³ and PE.^{24,25} These studies have interpreted negative D-dimer results with the results of other tests. Ginsberg et al²³ evaluated the results of a bedside, whole-blood agglutination D-dimer assay with impedance plethysmography in patients with suspected DVT. When both study results were negative, anticoagulation therapy was withheld and the patients were followed for 3 months. In this group of patients,

the negative predictive value was 98.5% (95% CI; range, 96.3% to 99.6%). For the D-dimer test alone, the negative predictive value was 97.2%. Currently, the authors of this article do not rely on the ELISA D-dimer test alone to exclude PE; however, as laboratory techniques improve and the speed with which these tests can be performed increases, D-dimer testing may become more useful for excluding PE, especially when used in conjunction with other noninvasive testing.

Both DVT and PE management studies have been performed with therapeutic decisions based, in part, on D-dimer results. Perrier et al^{24,25} conducted several management studies incorporating the ELISA D-dimer test into the diagnostic approach to acute PE. Each patient was managed using a diagnostic protocol, including an assessment of clinical probability, V/Q scan, ELISA plasma D-dimer, and lower extremity ultrasonography. In their first study, PE was ruled out in 48 patients who had a nondiagnostic lung scan together with low clinical probability.²⁴ In 53 cases, PE was ruled out by a quantitative D-dimer test result of less than 500 µg/L. Only 77 of 202 patients with nondiagnostic V/Q scans required pulmonary angiography. At 6-month follow-up, only two of 199 patients in whom the protocol had ruled out PE were diagnosed with a subsequent VTE event. Using the same cutoff value for the quantitative D-dimer test, these investigators subsequently reported that of 198 patients with suspected PE and a D-dimer level of less than 500 µg/L, 196 were free of PE, one had PE, and one was lost to follow-up. Thus, the negative predictive value of the D-dimer test was approximately 196 of 198 patients (99%). These data, although from one group of investigators, are very encouraging. Rapid bedside assays are becoming increasingly available and additional outcome studies will further define their role; however, the authors of this article do not currently recommend the D-dimer test, particularly in the absence of other supportive diagnostic studies, as a standard part of the PE or DVT diagnostic algorithm. An algorithm for the diagnostic approach to suspected PE is shown in **Figure 2**.

CONCLUSIONS

The diagnostic approach to patients with suspected PE is evolving. Recent data suggest that spiral CT and MRI are becoming sensitive and specific techniques for the detection of acute PE. These techniques may eventually replace V/Q scanning as the initial diagnostic test for patients with suspected PE if the sensitivity and specificity of these tests continues to improve and eventually approaches that of pulmonary angiography. Spiral CT offers the added advantage of excellent visualization of lung parenchymal and mediastinal structures whereas

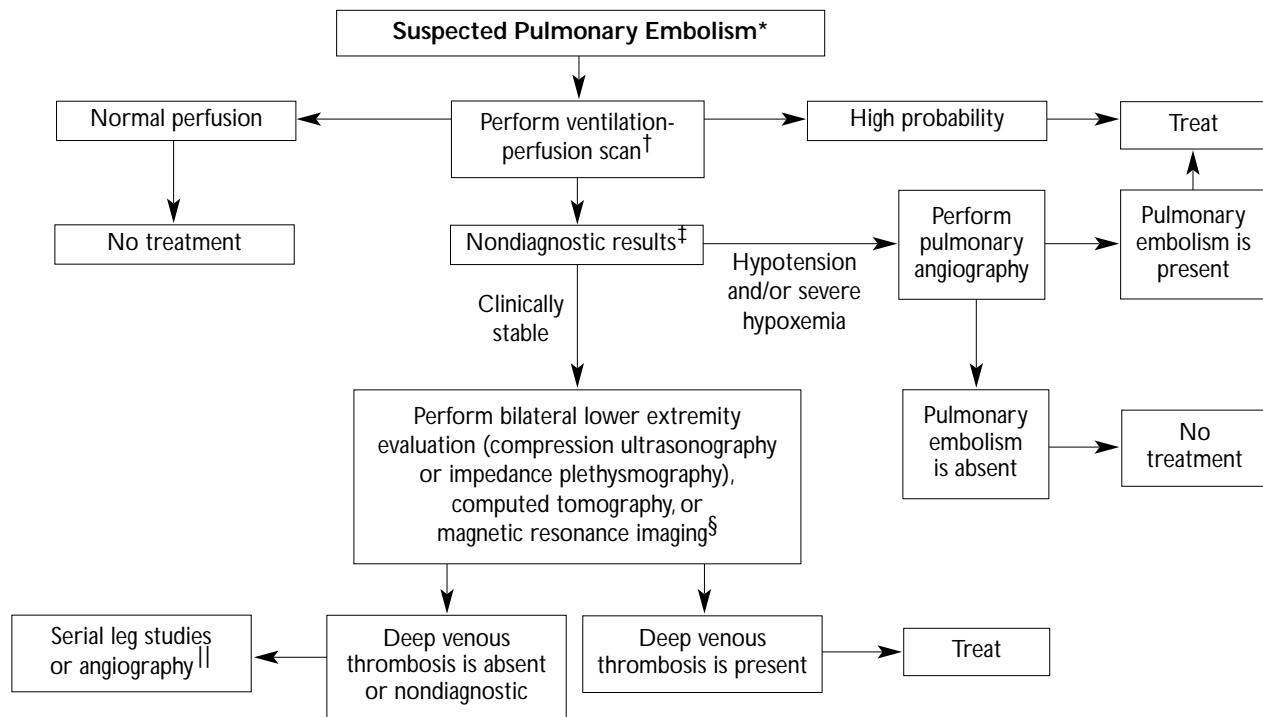


Figure 2. Suggested diagnostic algorithm for the approach to suspected pulmonary embolism.

*The history, physical examination, ancillary testing, and recognition of risk factors leading to the suspicion of pulmonary embolism (PE) are discussed in text. When PE is suspected and the risk of bleeding is determined to be low, it is appropriate to begin anticoagulation while diagnostic testing is performed.

†A ventilation-perfusion (V/Q) scan alone may suffice. Diagnostic alternatives to the V/Q scan include spiral computed tomography (CT) and magnetic resonance imaging (MRI). These modalities are increasingly used and require institutional and reader expertise and further validation in well-designed trials.

‡Patients with low probability V/Q scans and low clinical suspicion are unlikely to have PE; other patients require further evaluation. The physician has several options when V/Q scan, spiral CT, or lung MRI is nondiagnostic. Pulmonary angiography is the appropriate approach if the patient is unstable. Otherwise, leg studies can be performed. If spiral CT or lung MRI is performed, a negative result should be interpreted with the level of clinical suspicion. Although these techniques appear to be sensitive, additional studies (pulmonary angiography or leg studies) should be performed as appropriate.

§A positive test result on bilateral lower extremity evaluation is useful. The sensitivity for compression ultrasonography and impedance plethysmography is low in asymptomatic patients, and negative or nondiagnostic test results require additional data. MRI appears sensitive in this setting, but no level 1 data exist. The role of D-dimer testing in clinical algorithms is not clearly established, but recent data from some centers suggest that the sensitivity of certain assays may help exclude a venous thromboembolism event when they are combined with other diagnostic test results. General recommendations cannot yet be made.

|| Negative serial impedance plethysmography in this setting has been associated with excellent outcome without anticoagulation at certain centers.

MRI offers the potential to simultaneously diagnose PE and DVT. Both techniques may ultimately prove more cost-effective than current approaches by allowing a diagnostic algorithm tailored to a patient's specific presentation. For example, if clinical suspicion for DVT and PE is high, MRI may become the appropriate initial test to evaluate for both entities. Echocardiography is also being used more frequently in suspected PE, although this modality rarely eliminates the need for other diagnostic testing. Data from D-dimer management studies are very encouraging. Rapid bedside assays will become increasingly available and additional outcome studies will further define their role. **HP**

REFERENCES

- Giuntini C, DiRicco G, Marini C, et al: Pulmonary embolism: epidemiology. *Chest* 1995;107(suppl 1): 3S-9S.
- Dalen JE, Alpert JS: Natural history of pulmonary embolism. *Prog Cardiovasc Dis* 1975;17:257-270.
- Value of the ventilation/perfusion scan in acute pulmonary embolism: results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). The PIOPED Investigators. *JAMA* 1990;263:2753-2759.
- Stein PD, Athanasoulis C, Alavi A, et al: Complications and validity of pulmonary angiography in acute pulmonary embolism. *Circulation* 1992;85:462-469.
- Goldhaber SZ, Hennekens CH, Evans DA, et al: Factors associated with the correct antemortem diagnosis of major pulmonary embolism. *Am J Med* 1982;73: 822-826.
- Green RM, Meyer TJ, Dunn M, Glassroth J: Pulmonary embolism in younger adults. *Chest* 1992;101:1507-1511.
- The urokinase pulmonary embolism trial: a national cooperative study. *Circulation* 1973;47(suppl 2): II1-II108.
- Stein PD, Terrin ML, Hales CA, et al: Clinical, laboratory, roentgenographic, and electrocardiographic findings in patients with acute pulmonary embolism and no pre-existing cardiac or pulmonary disease. *Chest* 1991;100:598-603.
- McNeil BJ, Hessel SJ, Branch WT, et al: Measures of clinical efficacy: III. The value of the lung scan in the evaluation of young patients with pleuritic chest pain. *J Nucl Med* 1976;17:163-169.
- Stein PD, Hull RD, Pineo G: Strategy that includes serial noninvasive leg tests for diagnosis of thromboembolic disease in patients with suspected acute pulmonary embolism based on data from PIOPED. Prospective Investigation of Pulmonary Embolism Diagnosis. *Arch Intern Med* 1995;155:2101-2104.
- Remy-Jardin M, Remy J, Wattinne L, Giraud F: Central pulmonary thromboembolism: diagnosis with spiral volumetric CT with single-breath-hold technique: comparison with pulmonary angiography. *Radiology* 1992;185:381-387.
- Remy-Jardin M, Remy J, Deschildre F, et al: Diagnosis of acute pulmonary embolism with spiral CT: comparison with pulmonary angiography and scintigraphy. *Radiology* 1996;200:699-706.
- van Rossum AB, Treurniet FE, Kieft GJ, et al: Role of spiral volumetric computed tomographic scanning in the assessment of patients with clinical suspicion of pulmonary embolism and an abnormal ventilation/perfusion scan. *Thorax* 1996;51:23-28.
- Sostman HD, Layish DT, Tapson VF, et al: Prospective comparison of helical CT and MR imaging in clinically suspected acute pulmonary embolism. *J Magn Reson Imaging* 1996;6:275-281.
- Goodman LR, Curtin JJ, Mewissen MW, et al: Detection of pulmonary embolism in patients with unresolved clinical and scintigraphic diagnosis: helical CT versus angiography. *AJR Am J Roentgenol* 1995;164: 1369-1374.
- Mayo JR, Remy-Jardin M, Muller NL, et al: Pulmonary embolism: prospective comparison of spiral CT with ventilation-perfusion scintigraphy. *Radiology* 1997;205:447-452.
- Ferretti GR, Bosson JL, Buffaz PD, et al: Acute pulmonary embolism: role of helical CT in 164 patients with intermediate probability at ventilation-perfusion scintigraphy and normal results at duplex US of the legs. *Radiology* 1997;205:453-458.
- Grist TM, Sostman HD, MacFall JR, et al: Pulmonary angiography with MR imaging: preliminary clinical experience. *Radiology* 1993;189:523-530.
- Meaney JF, Weg JG, Chenevert TL, et al: Diagnosis of pulmonary embolism with magnetic resonance angiography. *N Engl J Med* 1997;336:1422-1427.
- Come PC: Echocardiographic evaluation of pulmonary embolism and its response to therapeutic interventions. *Chest* 1992;101:151S-162S.
- McConnell MV, Solomon SD, Rayan ME, et al: Regional right ventricular dysfunction detected by echocardiography in acute pulmonary embolism. *Am J Cardiol* 1996; 78:469-473.
- Bounameaux H, Cirafici P, de Moerloose P, et al: Measurement of D-dimer in plasma as diagnostic aid in suspected pulmonary embolism. *Lancet* 1991;337: 196-200.
- Ginsberg JS, Kearon C, Douketis J, et al: The use of D-dimer testing and impedance plethysmographic examination in patients with clinical indications of deep venous thrombosis. *Arch Intern Med* 1997;157: 1077-1081.
- Perrier A, Bounameaux H, Morabia A, et al: Diagnosis of pulmonary embolism by a decision analysis-based strategy including clinical probability, D-dimer levels, and ultrasonography: a management study. *Arch Intern Med* 1996;156:531-536.
- Perrier A, Desmarais S, Goehring C, et al: D-dimer testing for suspected pulmonary embolism in outpatients. *Am J Respir Crit Care Med* 1997;156:492-496.

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