Diagnosis of pulmonary embolism

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Abstract

NO SINGLE NONINVASIVE TEST for pulmonary embolism is both sensitive and specific. Some tests are good for "ruling in" pulmonary embolism (e.g., helical CT) and some tests are good for "ruling out" pulmonary embolism (e.g., D-dimer); others are able to do both but are often nondiagnostic (e.g., ventilation–perfusion lung scanning). For optimal efficiency, choice of the initial diagnostic test should be guided by clinical assessment of the probability of pulmonary embolism and by patient characteristics that may influence test accuracy. This selective approach to testing enables pulmonary embolism to be diagnosed or excluded in a minimum number of steps. However, even with the appropriate use of combinations of noninvasive tests, it is often not possible to definitively diagnose or exclude pulmonary embolism at initial presentation. Most of these patients can be managed safely without treatment or pulmonary angiography by repeating ultrasound testing of the proximal veins after one and 2 weeks to detect evolving deep vein thrombosis. Helical CT and MRI are rapidly improving as diagnostic tests for pulmonary embolism and are expected to become central to its evaluation.

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Objective testing for pulmonary embolism is crucial, because clinical assessment alone is unreliable and the consequences of misdiagnosis are serious. Failure to diagnose pulmonary embolism is associated with high mortality,[1,2] and incorrect diagnosis of the condition unnecessarily exposes patients to the risks of anticoagulant therapy. This review will outline approaches to the diagnosis of pulmonary embolism that minimize the use of pulmonary angiography, based on 2 guiding principles. In order for a test, or combination of tests, to be considered accurate enough to *diagnose the presence of pulmonary embolism*, it should have a positive predictive value of 85%. To *exclude the presence of pulmonary embolism*, such a test should have a negative predictive value of 95%, as compared with pulmonary angiography, or be associated with no more than a 2% frequency of venous thromboembolism during follow-up if it is the basis for withholding treatment.

Aspects of the epidemiology and natural history of venous thromboembolism that are relevant to the optimal selection and interpretation of diagnostic tests for pulmonary embolism are listed in Box 1.[3–50] The presence of risk factors identifies patients in whom it is appropriate to have a low threshold for the investigation of pulmonary embolism.[51,52] Some risk factors, such as previous venous thromboembolism,[53,54] recent surgery,[53,54] malignant disease[53] and advanced age,[54] help to discriminate between those with, and without, pulmonary embolism.

The sequential course of venous thromboembolism, with progression from the stages of deep vein thrombosis in the calf to proximal deep vein thrombosis and subsequently to pulmonary embolism,[2,52] has a number of important diagnostic and management implications. First, identifying asymptomatic deep vein thrombosis can, indirectly, establish the diagnosis of pulmonary embolism; this is very helpful when initial tests for pulmonary embolism are nondiagnostic.[20,55] Second, if proximal deep vein thrombosis can be excluded, there is a low short-term risk of pulmonary embolism among patients with nondiagnostic tests at presentation.[56–58] Third, if proximal deep vein thrombosis is excluded at presentation and does not develop within 2 weeks, patients with nondiagnostic tests for pulmonary embolism have a low long-term risk of subsequent venous thromboembolism.[56–58]

Clinical assessment

Clinical assessment is considered here within the framework of diagnostic tests that influence the probability of pulmonary embolism.[59–61] Approaches to clinical assessment of pulmonary embolism have fallen into 2 categories: (1) empirical (nonstandardized)[59–62] and, more recently, (2) standardized clinical models or prediction rules.[53,54,57]

Empirical clinical assessment

In the PIOPED and McMaster studies,[59,60] which assessed the accuracy of ventilation–perfusion lung scanning, the clinical probability of pulmonary embolism was categorized as either low, intermediate or high, based on history, physical examination, chest radiograph, electrocardiogram, and either impedance plethysmography of the legs[60] or arterial blood gases.[59] The prevalence of pulmonary embolism in each of these clinical probability categories, established by pulmonary angiography in patients with abnormal perfusion scans, was 15%, 38% and 79% in the McMaster study[60] and 9%, 30% and 68% in the PIOPED study.[59] In the Pisa-PED study, which was similar to the McMaster and PIOPED studies but assessed the accuracy of perfusion scanning alone and performed pulmonary angiography less consistently, the prevalence of pulmonary embolism was reported as 9%, 47% and 91% for the low, intermediate and high clinical probability categories.[61] More recently, using

Box 1: Components of the natural history of venous thromboembolism

- Most cases of deep vein thrombosis (DVT) (about 90%) start in the calf.[3–6]
- Isolated DVT of the calf:
  (i) rarely causes leg symptoms (80% of the cases of symptomatic DVT involve the proximal veins);[5,7]
  (ii) rarely causes clinically important pulmonary embolism.[3,7,8]
- About one-quarter of untreated cases of DVT in the calf will extend to involve the proximal veins:[9–11]
  (i) most cases of DVT in the calf that extend to involve the proximal veins do so within a week of presentation.[7,9,10,12]
- Most patients with symptomatic proximal DVT and without chest symptoms have lung scan evidence of pulmonary embolism (about 40% have "high-probability" lung scans[13–18]). These abnormalities are often misdiagnosed as new pulmonary embolism during treatment.[18,19]
- About 75% of all patients who are diagnosed with pulmonary embolism have DVT; about two-thirds of these cases involve the proximal veins:[20–24]
  (i) patients with less extensive pulmonary embolism are less likely to have proximal DVT;[25]
  (ii) up to one-quarter of patients with symptomatic pulmonary embolism have clinical evidence of DVT.[7,22,26]
- Elevated levels of D-dimer occur in most patients with symptomatic pulmonary embolism, and the degree of elevation is proportional to the extent of pulmonary embolism.[25,27,28]
- About 20% of symptomatic pulmonary embolism cases are confined to the subsegmental pulmonary arteries; [27,29–31] this proportion is expected to be larger in patients with pulmonary embolism and nondiagnostic lung scans.[29,30]
- About 50% of symptomatic pulmonary embolism cases involve the lobar or main pulmonary arteries.[29,30]
- Without treatment, about one-half of patients with symptomatic proximal DVT or pulmonary embolism are expected to have recurrent venous thromboembolism within 3 months.[32,33]
- After pulmonary embolism, as compared with DVT, at least within the first 3 months, a high proportion of recurrent episodes of venous thromboembolism are pulmonary embolism and are fatal (case-fatality rate over 2-fold higher).[34,35]
- 10% of symptomatic pulmonary embolism cases are estimated to be fatal within an hour of first symptoms:[36,37]
  (i) 5%–10% of patients with pulmonary embolism have shock at presentation;[38,39]
  (ii) about 50% of patients who are diagnosed with pulmonary embolism have echocardiographic evidence of right ventricular dysfunction at presentation, a finding that is associated with an elevated short-term mortality.[38–41]
- With treatment of pulmonary embolism, about 50% resolution of perfusion defects is expected after 2–4 weeks.[40,42–45] Eventually, complete resolution of pulmonary embolism is expected to occur in about two-thirds of patients.[46–48]
- With treatment of proximal DVT, residual thrombosis is evident on ultrasound scans in about half of patients after 1 year.[49,50]

mostly noninvasive tests as the criterion standard, Perrier and colleagues recorded prevalences of pulmonary embolism of 8%, 36% and 67% based on empirical clinical assessment.[62]

Standardized clinical assessment

Three research groups have recently published explicit prediction rules for determining the clinical probability of pulmonary embolism.[53,54,57,63] Wells and colleagues used an assessment of symptoms and signs, the presence of an alternative diagnosis to account for the patient's presentation and the presence of risk factors for venous thromboembolism to categorize a patient as having low, intermediate or high probability of pulmonary embolism.[57] A simplified version of their original model (Box 2) yielded a prevalence of pulmonary embolism of 2% in low-probability (40% of patients), 19% in intermediate-probability (52% of patients) and 50% in high-probability (8% of patients) categories.[53] This clinical model has been prospectively validated by its use, in conjunction with other tests, to manage outpatients with suspected pulmonary embolism successfully (see later).[58] The Pisa-PED group used an assessment of symptoms and chest radiograph and electrocardiogram findings to divide patients into either high-probability (92% prevalence of pulmonary embolism) or low-probability (11% prevalence of pulmonary embolism) categories.[63] These investigators then proposed a 3-category clinical model, based on these criteria and the presence of an alternative diagnosis, to account for the patient's symptoms.[63] They subsequently reported that this model yielded prevalences of pulmonary embolism in the low-probability, intermediate-probability and high-probability groups of 2%, 50% and 100%.[64] Based on data from 2 prospective studies, Perrier and colleagues[65,66] derived a continuous scoring system for the probability of pulmonary embolism that included 8 clinical, blood gas or chest radiograph variables.[54] When scores were partitioned into 3 probability categories, the associated prevalences of pulmonary em-

bolism were 10%, 38% and 81%, similar to the results that these investigators obtained using empirical assessment.[54] It is important to note that standardized clinical models for the probability of pulmonary embolism may have lower predictive values when used in a setting other than that in which they were derived.[67] Differences among centres in the mix of patients who are referred for diagnostic testing may influence the discriminatory value of clinical variables and partly account for this.[54,67,68]

In summary, there is good evidence that clinical assessment, either empirical or standardized, can stratify patients' probability of having pulmonary embolism. The prevalence of pulmonary embolism is expected to be ≤ 10% in patients with a low clinical probability, about 25% in the intermediate-probability group and ≥ 60% in the high clinical probability group.

D-dimer blood testing

D-dimer is formed when cross-linked fibrin is lysed by plasmin, and elevated levels usually occur with pulmonary embolism.[69] However, because elevations of D-dimer are nonspecific (e.g., increased by aging, inflammation, cancer), an abnormal result has a low positive predictive value.[69] The value of D-dimer is that a negative result can help to exclude pulmonary embolism. There are a wide variety of D-dimer assays, some of which are not suitable as diagnostic tests for pulmonary embolism because they have such poor operating characteristics (i.e., they are inaccurate).[69] D-dimer assays that have been validated as tests for pulmonary embolism vary in their sensitivity and specificity, partly because of differences in their accuracy and partly because of the cutoff value they use to define normality (i.e., trade-off between sensitivity and specificity). In practice, depending largely on their sensitivity and associated negative likelihood ratio, D-dimer assays that are valid diagnostic tests for pulmonary embolism can be divided into 2 categories.

Very highly sensitive D-dimer tests

These D-dimer assays have a sensitivity for venous thromboembolism of about 98% or higher.[66,69] Their negative likelihood ratio is high enough to "rule out" pulmonary embolism in all patients and, consequently, these assays can be used as a "stand-alone" test for the exclusion of pulmonary embolism.[66] However, these assays generally have a low specificity (about 40%) and a high frequency of false-positive results (e.g., 53%),[66] which reduces their clinical usefulness. Many conventional enzyme-linked immunosorbent assay (ELISA) D-dimer assays (cut-off of about 500 fibrinogen-equivalent units/mL) fall into this category, but they are not suitable as diagnostic tests because they have a slow turnaround time and require batch analysis.[69] "Rapid" ELISA D-dimer assays have recently been developed.[69] Perrier and colleagues have shown that one such assay (Vidas DD, bioMérieux, Marcy l'Étoile, France), the results of which were normal in 36% of consecutive outpatients with suspected pulmonary embolism, had a negative predictive value of 100% for subsequent symptomatic venous thromboembolism.[66]

Moderate-to-highly sensitive D-dimer tests

These D-dimer assays have a sensitivity for venous thromboembolism of about 85%–98%.[69] The negative likelihood ratio and predictive value with these tests are not high enough to rule out pulmonary embolism in consecutive patients. Consequently, a normal result needs to be combined with another assessment that identifies patients as having a lower pretest probability for pulmonary embolism (e.g., low clinical probability,[58,70] nondiagnostic lung scan,[58,70] high alveolar dead space fraction[77,78]). Although neither test on its own can rule out pulmonary embolism, this is achieved by using the 2 tests in combination (Box 3). Such D-dimer assays are more specific than very sensitive D-dimer assays and, therefore, generate fewer false-positive results (e.g., 32%).[70] A whole-blood D-dimer assay (SimpliRED, Agen Biomedical, Brisbane, Australia), which can be performed at the bedside in minutes, is one such test that has been extensively evaluated (approximate sensitivity 85%, approximate specificity 70%).[58,70,78,79]

Box 2: Model for determining the clinical probability of pulmonary embolism[53]

Variable	Points
Clinical signs and symptoms of DVT (leg swelling and pain with palpation of the deep veins)	3.0
An alternative diagnosis is less likely than pulmonary embolism	3.0
Heart rate > 100 beats/minute	1.5
Immobilization or surgery in the previous 4 weeks	1.5
Previous DVT/pulmonary embolism	1.5
Hemoptysis	1.0
Malignancy (treatment ongoing or within previous 6 months or palliative)	1.0
Total points	___

Pretest probability calculated as follows:	Total points
High	> 6
Moderate	2–6
Low	< 2

Ventilation–perfusion lung scanning

Ventilation–perfusion lung scanning has been the usual initial investigation in patients with suspected pulmonary embolism. A normal perfusion scan excludes pulmonary embolism,[74,75,80,81] but is found in a minority (about 25%) of patients.[21,55,57,59,61,76] Perfusion defects are nonspecific, however, with only about one-third of patients with defects having pulmonary embolism.[55,59–61,76,81] The probability that perfusion defects are due to pulmonary embolism increases with increasing size and number, the presence of a wedged shape and the presence of a normal ventilation scan ("mismatched" defect).[59–61] Mismatched perfusion defects that are segmental or larger are termed "high-probability" defects.[60] A single mismatched defect is associated with a prevalence of pulmonary embolism of about 80%, whereas this prevalence is ≥ 90% with 3 or more defects.[82] High-probability scans occur in about 50% of patients with pulmonary embolism[59,60] and about 10% of patients who are tested for pulmonary embolism.[57,59,60,83] Therefore, about 65% of patients with suspected pulmonary embolism have intermediate-probability or lower-probability lung scans (see later) and require further testing.[57,59,60,83]

Box 3: Test results that effectively confirm or exclude the presence of pulmonary embolism

Pulmonary embolism is confirmed by

Pulmonary angiography: intraluminal filling defect

Helical CT: intraluminal filling defect in a lobar or main pulmonary artery[71,72]

Ventilation–perfusion scan: high-probability scan and moderate/high clinical probability[21,59]

Diagnostic tests for DVT: evidence of acute DVT with nondiagnostic ventilation–perfusion scan or helical CT[55]

Pulmonary embolism is excluded by

Pulmonary angiogram: normal[73]

Perfusion scan: normal[74,75]

D-dimer test: normal test that has very high sensitivity (≥ 98%) and at least moderate specificity (≥ 40%)[66]

Normal D-dimer that has at least moderately high sensitivity (≥ 85%) and specificity (≥ 70%) AND
(a) low clinical suspicion for pulmonary embolism[58,70,76] OR
(b) normal alveolar dead space fraction[77,78]

Nondiagnostic ventilation–perfusion scan or normal helical CT, and normal proximal venous ultrasound scans AND
(a) low clinical suspicion for pulmonary embolism[58,62] OR
(b) normal D-dimer test that has at least moderately high sensitivity (≥ 85%) and specificity (≥ 70%)[58,70]

Computed tomography

Traditional computed tomography (CT) is not suitable for evaluating suspected pulmonary embolism, because it is not feasible to opacify the pulmonary arteries with radiographic contrast for the time required to complete imaging (about 3 minutes) and, even if this could be achieved, motion artifact would interfere with image quality. These problems are overcome by helical CT (also known as spiral or continuous volume CT) as image acquisition can be completed within a single breath hold (e.g., about 20 seconds).[84,85] Although helical CT is widely used in clinical practice, 2 recent systematic reviews of studies that evaluated the accuracy of helical CT for the diagnosis of pulmonary embolism concluded that the technique has been inadequately evaluated for this purpose.[71,86] Since these reviews, 2 studies have helped to clarify the accuracy, strengths and limitations of helical CT for the diagnosis of pulmonary embolism.[72,85,87] In the first, among 299 patients who did not have pulmonary embolism excluded by a negative highly sensitive D-dimer result (pulmonary embolism prevalence of 39%), helical CT had a sensitivity of 70%, a specificity of 91%, a positive likelihood ratio of 8.0, a negative likelihood ratio of 0.3, an overall positive predictive value of 84% and a negative predictive value of 82%.[72] The positive predictive value of CT varied by anatomical level: 100% in main pulmonary arteries, 85% in lobar and only 62% in segmental (16% abnormal CT results) pulmonary arteries. Subsegmental pulmonary arteries were not systematically evaluated in this study.[72] In the second study, which prospectively compared helical CT to diagnostic lung scanning (normal or high-probability scans) or pulmonary angiography in 230 patients, helical CT had sensitivities of 86% for segmental or larger pulmonary embolisms and 21% for subsegmental pulmonary embolisms (21% of total pulmonary embolisms).[85,87] Overall sensitivity for pulmonary embolism was 69% and specificity was 86%.[85,87]

The combined results from a number of studies suggest that the sensitivity of helical CT for isolated subsegmental pulmonary embolism is about 30%[86,87] and that such emboli account for about 20% of symptomatic pulmonary embolism.[29–31,86,88,89] Because patients with isolated subsegmental pulmonary embolism are also likely to have a substantial risk of recurrence, these emboli cannot be dismissed as clinically unimportant.

Taken together, these findings suggest the following results with helical CT. First, intraluminal filling defects in lobar or main pulmonary arteries have a positive predictive value for pulmonary embolism of at least 85% and can be interpreted in the same way as a high-probability ventilation–perfusion scan. Second, intraluminal defects that are confined to segmental, and particularly subsegmental, pulmonary arteries are nondiagnostic and require further testing. Third, a normal helical CT substantially reduces the probability of pulmonary embolism but does not exclude

this diagnosis (i.e., is similar to a "low-probability" ventilation–perfusion scan). A frequency of pulmonary embolism of about 5%, during follow-up or at pulmonary angiography, in patients with nondiagnostic lung scans, normal helical CT scans and normal venous ultrasonography emphasizes that a normal CT scan alone does not exclude pulmonary embolism.[72,90–92]

Magnetic resonance imaging (MRI) has been less well evaluated than helical CT for the diagnosis of pulmonary embolism; however, it appears to have similar accuracy.[31,93–95] Both helical CT and MRI have the advantage that they may reveal an alternative pulmonary diagnosis, and both examinations may be extended to look for concomitant deep vein thrombosis. MRI also avoids exposure to radiation and radiographic contrast. It is anticipated that the diagnosis of pulmonary embolism by CT and MRI will continue to improve, and modern scanners may already be more accurate than those used in published studies using older technology.[85]

Tests for deep vein thrombosis

Detection of asymptomatic deep vein thrombosis is an indirect way to diagnose pulmonary embolism.[20,55] In the presence of acute pulmonary embolism, deep vein thrombosis is detectable by bilateral ascending venography in about 75%[21–23] of patients and by compression ultrasonography of the proximal veins in about 50%[21,25] of patients (i.e., sensitivity for pulmonary embolism of 75% and 50% respectively). However, among patients with symptomatic pulmonary embolism, there are strong correlations among (1) pulmonary embolism size, (2) the presence of diagnostic findings on ventilation–perfusion scanning or helical CT and (3) the presence of proximal deep vein thrombosis.[25] Consequently, the proportion of patients with pulmonary embolism and nondiagnostic findings on ventilation–perfusion scanning (or helical CT) who will have detectable deep vein thrombosis will be lower than the values noted previously (about 30% for compression ultrasonography of the proximal veins).[25,55]

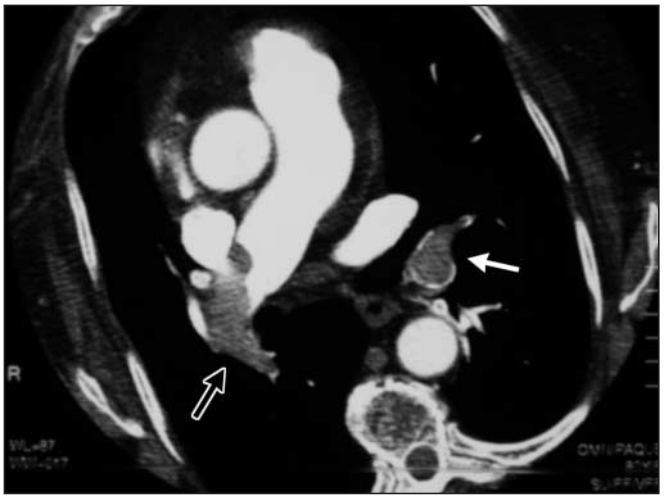
In practice, ultrasonography of the proximal veins is abnormal in about 5% of patients who have nondiagnostic lung scans.[55,57,58,62,76,83] This ultrasound examination can be limited to an assessment of venous compressibility at the inguinal ligament and the mid-popliteal fossa without loss of sensitivity for proximal deep vein thrombosis.[96] Because the positive predictive value of an abnormal ultrasound scan is only about 75% in this setting, confirmatory venography should be considered in patients who are more likely to have a false-positive result (e.g., less convincing ultrasound findings, previous venous thromboembolism with the potential for residual abnormalities, negative D-dimer).[20,55] Normal bilateral proximal venous ultrasound scans or venograms do not rule out embolism in patients with nondiagnostic lung scans (or helical CT); however, they reduce this probability (negative likelihood ratios of about 0.7 for ultrasonography and about 0.5 for venography). Because absence of deep vein thrombosis is associated with a lower risk of recurrence among patients with pulmonary embolism,[20,23,97] the negative likelihood ratios for symptomatic venous thromboembolism during follow-up with negative tests for deep vein thrombosis are expected to be lower than these estimates.

Pulmonary angiography

Pulmonary angiography is the criterion standard for the diagnosis of pulmonary embolism, but it is associated with serious side effects (e.g., mortality of about 0.5%),[73] is technically demanding to perform, may be difficult to interpret and is costly. It is contraindicated in patients with renal impairment and may not be feasible in the sickest patients.[59,60] For these reasons, pulmonary angiography is usually reserved for patients who have had nondiagnostic noninvasive tests for pulmonary embolism when it is considered unsafe to withhold anticoagulation, while performing serial testing to detect evolving proximal deep vein thrombosis (see later), or when it is necessary to establish a diagnosis to manage patients with severe symptoms (Box 4). Of patients with normal pulmonary angiograms, about 1% have an episode of symptomatic venous thromboembolism during the following 6 months;[73,98] this is the standard against which the safety of withholding anticoagulant therapy following negative tests for pulmonary embolism is assessed.

Echocardiography

Transthoracic or transesophageal echocardiography may directly visualize embolized thrombi (right heart chambers or central pulmonary arteries) or show right heart hemodynamic changes that indirectly suggest pulmonary em-



Helical CT of the pulmonary arteries with intraluminal filling defects in the lobar artery of the left lower lobe (solid arrow) and the main artery of the right lung (open arrow) in a patient with a chest deformity.

bolism.[99] Indirect parameters such as unexplained right ventricular dilatation/dysfunction and marked tricuspid regurgitation, which can be detected similarly by transthoracic and transesophageal echocardiography, have a sensitivity of about 50% and a specificity of about 90% for pulmonary embolism.[64,100–103] Transthoracic echocardiography visualizes intracardiac thrombi (usually right atrium) in about 5% of patients with acute pulmonary embolism and generally does not detect emboli in the pulmonary arteries.[38,64,100–102] Transesophageal echocardiography can visualize thrombi in the central pulmonary arteries (main, right, proximal portion of left) with high specificity (> 90%),[101,104] but its sensitivity has not been evaluated in unselected patients with pulmonary embolism (perhaps about 30%).

Because of the limited specificity with the transthoracic approach, the invasiveness of the transesophageal approach and the low sensitivity with both approaches, echocardiography is not suitable as a routine diagnostic test for pulmonary embolism. However, echocardiography shows indirect evidence of pulmonary embolism in about 80% of patients with massive embolism (i.e., ≥ 60% perfusion defects),[100] and central emboli can be seen by transesophageal echocardiography in about 70% of the patients who have pulmonary embolism and right ventricular dysfunction.[101,104,105] Consequently, echocardiography is valuable in differentiating between massive pulmonary embolism and other causes of hemodynamic compromise. In conjunction with clinical assessment and the results of other noninvasive tests (e.g., venous ultrasonography), echocardiography may enable pulmonary embolism to be diagnosed, or anticoagulants to be withheld, in severely ill patients, at least until it becomes feasible to perform additional testing.[100] In addition to its diagnostic role, the echocardiographic finding of right ventricular dysfunction or patent foramen ovale in conjunction with pulmonary embolism indicates a relatively poor short-term prognosis and may encourage the use of more aggressive therapy for pulmonary embolism.[2,38,99,106]

Box 4: Management of patients who have had nondiagnostic noninvasive tests at presentation

Serial venous ultrasonography of the proximal veins (after 1 and 2 weeks)

This is suitable for most such patients,[57,58] although pulmonary angiography is generally preferred for the subgroups outlined below. Another option is to perform bilateral venography before serial venous ultrasonography (i.e., for patients who might otherwise be considered for pulmonary angiography).[23]

Pulmonary angiography is the preferred option in the following settings:

- Segmental intraluminal filling defect on helical CT*†
- Subsegmental intraluminal filling defect on helical CT and high clinical probability of pulmonary embolism†
- High-probability ventilation–perfusion scan and low clinical suspicion†
- Severe symptoms, moderate post-test probability and a need to exclude pulmonary embolism from the differential diagnosis
- Serial testing not feasible (e.g., patient scheduled for surgery, geographic inaccessibility)

*A segmental intraluminal filling defect with high clinical suspicion is likely to have a positive predictive value of ≥ 85% and could be considered diagnostic for pulmonary embolism. This may also be true with good-quality "unequivocal" images obtained with a modern scanner when there is a moderate clinical suspicion.

†Ventilation–perfusion scanning can be performed having obtained these findings with helical CT, or helical CT may be performed having obtained these findings with ventilation–perfusion scanning. The second test may be diagnostic for pulmonary embolism.[30,71,72,90–92] If the second test is also nondiagnostic for pulmonary embolism, serial ultrasonography may be reconsidered.

Combinations of diagnostic tests for pulmonary embolism

When individual tests are nondiagnostic, it may be possible to combine their results to confirm or exclude pulmonary embolism (Box 3). Some of the better studied combinations are described below.

Clinical assessment and ventilation–perfusion lung scanning

The clinical assessment of pulmonary embolism is complementary to ventilation–perfusion lung scanning. A high-probability lung scan with a moderate or high clinical probability of pulmonary embolism is diagnostic (prevalence of pulmonary embolism of ≥ 90%).[59,60] All other combinations of clinical probability and abnormal lung scan findings are associated with a prevalence of pulmonary embolism of 10%–50% and, therefore, require further investigation.[59,60] Among the patients with these other combinations, the prevalence of pulmonary embolism varies as follows: about 50% with a low clinical suspicion and a high-probability scan, about 10% with a low clinical suspicion and subsegmental, matched perfusion defects ("low-probability" scans) and about 25%, on average, with other combinations.[59,60]

Clinical assessment and negative D-dimer testing

The combination of a low clinical probability and a negative moderately sensitive D-dimer assay (sensitivity ≥ 85%) has a negative predictive value for pulmonary embolism of about 99%.[58,70,76] Two management studies have confirmed the safety of excluding pulmonary embolism with this combination of findings.[58,76]

Nondiagnostic lung scanning and negative D-dimer testing

The combination of a nondiagnostic lung scan (i.e., an abnormal lung scan result lower than high probability) and a normal moderately sensitive D-dimer assay has been estimated to have a negative predictive value of about 97%.[70,76] This combination of findings is currently considered nondiagnostic, particularly if clinical probability is high.

Nondiagnostic lung scanning and normal ultrasound testing for proximal deep vein thrombosis

In general, the combination of a nondiagnostic lung scan and normal bilateral tests for deep vein thrombosis at presentation is nondiagnostic. However, because the negative predictive value of low clinical suspicion, a nondiagnostic scan and normal proximal ultrasound examinations is expected to be about 95%,[57,58,62,66] and because there is evidence that patients with such results have a low (≤ 2%) risk of presenting with symptomatic venous thromboembolism during follow-up,[58,62] this combination of findings may be considered to exclude the presence of pulmonary embolism (some choose to perform serial venous ultrasonography [see later]).

Nondiagnostic lung scanning, negative D-dimer testing and normal ultrasound testing for proximal deep vein thrombosis

When this combination of findings includes a moderately sensitive D-dimer test, this is estimated to have a negative predictive value of about 98%.[58,70,76] Although this approach has not been well tested prospectively, excluding the presence of pulmonary embolism with this combination of findings is reasonable. However, serial venous ultrasonography should be considered when there is a high clinical probability of pulmonary embolism.

Helical CT scanning in combination with other tests

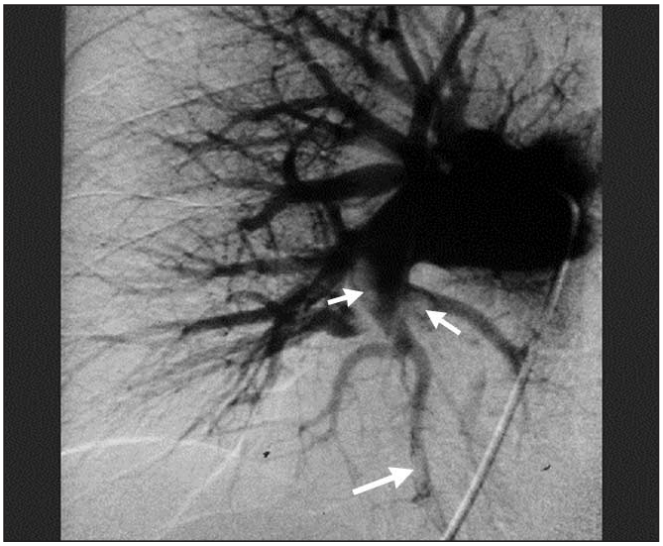
Based on the estimated prevalence of pulmonary embolism with different CT findings (see earlier) and extrapolating from studies that evaluated patients with nondiagnostic lung scans, various combinations of test results are expected to exclude the presence of pulmonary embolism when combined with a normal helical CT (Box 3).

Management of patients with nondiagnostic results of combined noninvasive tests

Depending on the tests that have been performed and local referral patterns, results of noninvasive testing are nondiagnostic in 30%–60% of the patients with suspected pulmonary embolism.[55–60,62,66,70,72,76] Overall, these patients have a prevalence of pulmonary embolism of about 20%,[55,57–60,66,70,72,76] which is too high to ignore and too low to treat. Pulmonary angiography can be performed in these patients[66,76] but adherence to this recommendation is poor.[107] An alternative is to forgo definitive testing for pulmonary embolism but to use knowledge of the predictable natural history of venous thromboembolism to manage patients in a way that is safe (Box 1). For most patients with initial nondiagnostic testing for pulmonary embolism that includes normal ultrasound scans of the proximal veins, this can be achieved by withholding treatment unless proximal deep vein thrombosis is detected on repeat ultrasound examinations during follow-up (Box 4).

Withholding anticoagulants and pulmonary angiography on the basis of serial normal ultrasounds of the proximal veins

The 20% of patients with initial nondiagnostic tests for pulmonary embolism (including normal bilateral proximal venous ultrasound scans) who have had the condition also have either small residual deep vein thrombosis (usually confined to the calf) or no residual deep vein thrombosis. These patients are at risk of recurrent pulmonary embolism if the small residual thrombi extend or if a new deep vein thrombosis forms, with the highest risk period being within 2 weeks of presentation.[32,33,66,98,108] However, before such patients have a recurrent episode of pulmonary embolism, they must first redevelop proximal deep vein thrombosis. Performing serial venous ultrasounds over a 2-week period in all patients with nondiagnostic tests for pulmonary embolism enables those who are progressing toward recurrent pulmonary embolism to be detected, and treated, before recurrent embolism.[20,56–58] Ultrasound scans of the proximal veins become abnormal during serial testing in about 2% of patients.[56–58] Those



Conventional pulmonary angiogram of the right lung with intraluminal filling defects in the lobar artery and segmental and subsegmental arteries of the lower lobe.

Box 5: Clinical situations that may alter diagnostic approach or test interpretation

In-hospital patients

Inpatients, especially after surgery,[111] often have increased D-dimer levels that markedly reduce the value of D-dimer testing (e.g., specificity of 7% in inpatients[81] versus 47% in outpatients[66]).

Treatment of presumptive pulmonary embolism

D-dimer levels are estimated to decrease about 25% after 24 hours of heparin therapy, and this is expected to reduce the sensitivity of D-dimer testing (e.g., from 96% to 89%).[112]

High clinical probability

D-dimer testing has little clinical utility in patients with a high clinical probability of pulmonary embolism, because specificity is lower in this group (e.g., 28% compared with 54% with low clinical probability) and the combination of a lower specificity and high prevalence of embolism results in a low frequency of negative D-dimer results (e.g., 17% compared with 51% with low probability), which have a lower negative predictive value (e.g., 77% compared with 100% with low probability).[113]

Previous venous thromboembolism

Imaging abnormalities associated with previous DVT or pulmonary embolism may persist and be misdiagnosed as recurrent venous thromboembolism (e.g., decrease in positive predictive value of a high-probability lung scan from 91% to 74% with a history of pulmonary embolism[59]).[7,59] In about half of patients with recently diagnosed DVT who present with suspected pulmonary embolism and have a high-probability lung scan, the abnormalities predate the onset of chest symptoms.[18,19]

Influence of age on accuracy of diagnostic tests

The specificity of D-dimer testing and lung scanning decreases with age (e.g., D-dimer specificity: 67% at ≤ 50 years versus 10% at ≥ 80 years;[24] proportion of lung scans that are nondiagnostic: 32% at ≤ 40 years versus 58% at ≥ 80 years[24]).[24,114]

Cardiopulmonary disease

Cardiopulmonary disease (particularly lung disease) is associated with a high proportion of nondiagnostic lung scans (e.g., 78% [91% with chronic obstructive lung disease] versus 64%[115]) and a lower positive predictive value with a high-probability defect (e.g., 83% versus 93%[62,116,117]).

Malignant disease

The presence of malignancy reduces the specificity of many tests for pulmonary embolism (e.g., D-dimer: 48% versus 82%)[118] and may also result in false-positive results (e.g., high-probability lung scans[119] or abnormal helical CTs[86] with intrathoracic malignancy).

Central venous catheters

The arms and central veins should be considered as a source for emboli and as a target for diagnostic testing in patients with central venous catheters who are suspected of having pulmonary embolism.[120]

Pregnancy

As compared with nonpregnant patients, the prevalence of pulmonary embolism among pregnant patients who are investigated for pulmonary embolism is low (about 5% versus about 20%)[110] and the prevalence of normal perfusion scans is high (about 70% versus about 25%[111]).[54,110]

who do not develop an abnormal ultrasound have a low subsequent risk of symptomatic venous thromboembolism that is similar to the rate observed following normal pulmonary angiography[58] (about 1% over 6 months).[56–58]

Clinical follow-up after completing diagnostic testing

After the presence of pulmonary embolism has been excluded or after serial ultrasonography has been completed in those who could not have pulmonary embolism excluded on the day of presentation, there remains a small risk of symptomatic venous thromboembolism within the next 3 months (about 1%).[57–59,66,72,76,98] Consequently, patients who are not diagnosed with pulmonary embolism should routinely be advised to return if they develop new symptoms suggestive of deep vein thrombosis or pulmonary embolism. Because most episodes of symptomatic venous thromboembolism that occur among these patients during follow-up are deep vein thrombosis or nonfatal pulmonary embolisms (e.g., 1 fatal pulmonary embolism among 16 events in 4 recent studies[57,58,66,76]), re-evaluation of patients with persistent or recurrent symptoms serves as an additional safety measure.

Diagnosis of pulmonary embolism in pregnancy

Pregnant patients with suspected pulmonary embolism can be managed similarly to nonpregnant patients, with the following modifications. First, ultrasonography of the proximal veins can be performed as an initial test; patients with unequivocal evidence of deep vein thrombosis can be presumed to have pulmonary embolism. Second, the amount of radioisotope used for the perfusion scan can be reduced and the duration of scanning extended. Third, if pulmonary angiography is performed, the brachial approach with abdominal screening is preferable to reduce fetal radiation exposure. Fourth, in the absence of safety data relating to helical CT in pregnancy, this is discouraged (if it is necessary, abdominal screening should be used).

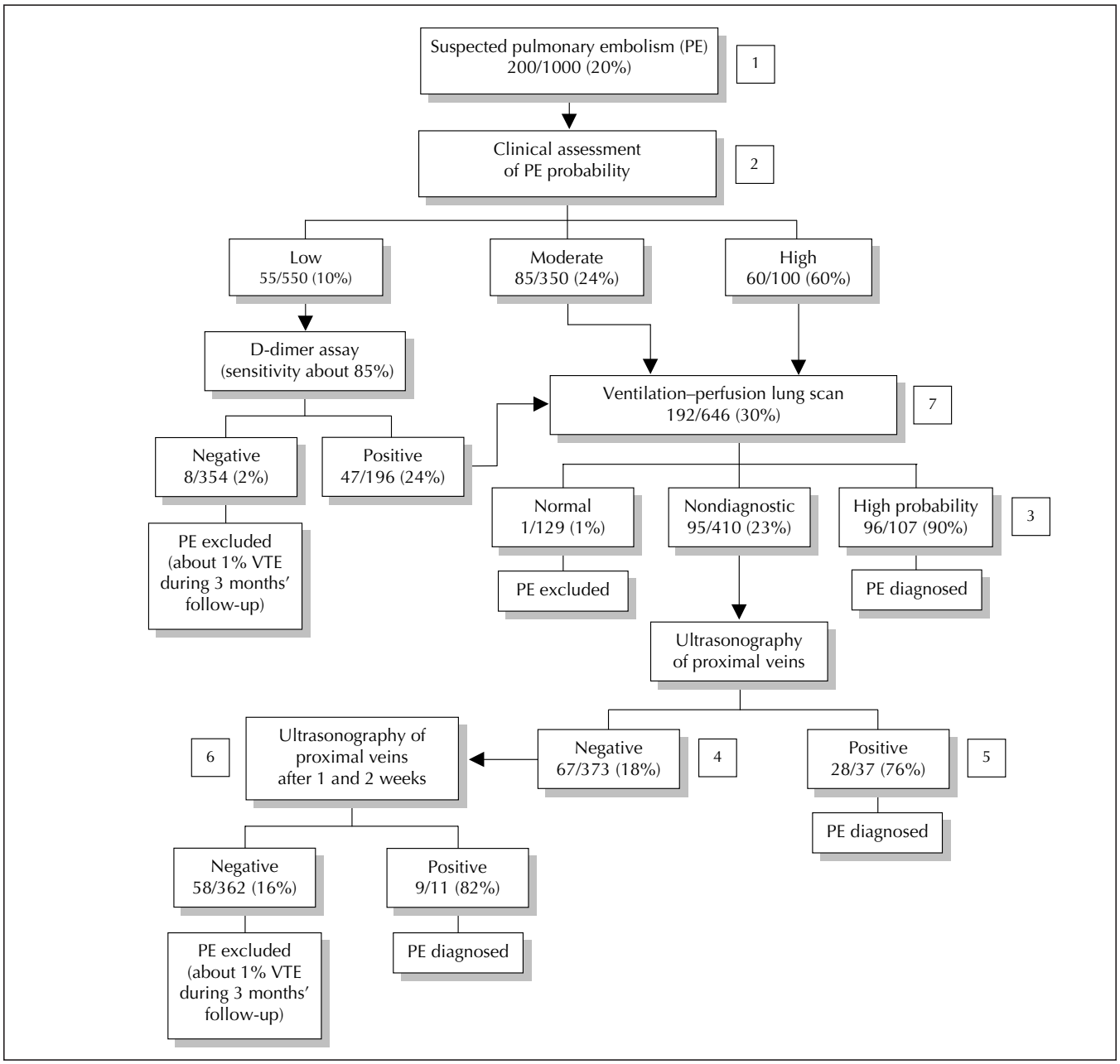


Fig. 1: A diagnostic algorithm for pulmonary embolism (estimated frequencies of test results and associated prevalences of pulmonary embolism for a hypothetical cohort of 1000 outpatients) [1]. If a very sensitive D-dimer assay is used, it can be the first test performed: a negative result excludes pulmonary embolism regardless of clinical assessment category and a positive test can be followed by a ventilation–perfusion scan [2]. A ventilation–perfusion scan can be performed as the initial test without using clinical assessment of the probability of pulmonary embolism as part of the diagnostic process [3]. Pulmonary angiography or helical CT may be considered if the clinical assessment of pulmonary embolism probability is low, particularly if a D-dimer test has not been done [4]. Additional testing (e.g., helical CT, bilateral venography) may be considered if overall assessment suggests a high probability of pulmonary embolism (e.g., 50%–80%), symptoms are severe or cardiopulmonary reserve is poor [5]. Venography should be considered if there is an increased risk of a false-positive ultrasound result (e.g., previous venous thromboembolism, equivocal ultrasound findings, preceding findings suggest low probability of pulmonary embolism [e.g., ≤ 10%]) [6]. It is reasonable not to repeat ultrasound testing, or to do only 1 more ultrasound after 1 week, if preceding findings suggest a low probability of pulmonary embolism (e.g., ≤ 10%) [7]. If helical CT is used in place of ventilation–perfusion lung scanning: (i) intraluminal filling defects in segmental or larger pulmonary arteries are generally diagnostic for pulmonary embolism; (ii) all other findings (i.e., a normal CT scan or intraluminal filling defects confined to the subsegmental pulmonary arteries) are nondiagnostic and can be managed as shown for a nondiagnostic lung scan.

It is likely that the risk of inaccurate diagnosis of pulmonary embolism during pregnancy far exceeds the risks of radiation exposure with diagnostic testing.[109,110] Recent studies indicate that the prevalence of pulmonary embolism tends to be low, and the frequency of normal lung scans high, in pregnant patients who are investigated for pulmonary embolism (Box 5[111–120]).[54,110]

Algorithms for the diagnosis of pulmonary embolism

There are many valuable tests (including clinical assessment) that may be used, singly or in combination, to confirm or exclude the presence of pulmonary embolism with a high degree of confidence (Box 3). Availability of testing and differences among patient presentations (Box 5) will influence the diagnostic approach used.

A number of prospectively validated algorithms have been published that emphasize the use of different initial noninvasive tests in conjunction with ventilation–perfusion lung scanning. These include structured clinical assessment and serial venous ultrasonography;[57] sensitive D-dimer assay, empirical clinical assessment and venous ultrasonography at presentation only;[66] and clinical assessment, moderately sensitive D-dimer assay and serial venous ultrasonography.[58] Based on these studies and others that have been discussed, such an algorithm is presented in Fig. 1. Algorithms that incorporate helical CT require further validation.

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