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Diagnosis of Pulmonary Embolism

Marc Rodger and Philip S. Wells
Department of Medicine, Ottawa Hospital and the University of Ottawa, Ottawa, Ontario, Canada

Abstract

Pulmonary embolism (PE) is a common, lethal yet treatable disease. The clinical diagnosis of PE remains to be a problem due to the nonspecific presenting signs, symptoms, electrocardiographic findings, arterial blood gas abnormalities and chest X-ray changes. Despite these nonspecific clinical findings, clinicians are adept at assigning pretest probability using overall clinical assessment. Clinical models have been developed to improve the accuracy of pretest probability assessment. D-dimers are becoming a widely available clinical tool useful in the diagnostic management of suspected PE. The limitations of the imaging modalities for PE [ventilation–perfusion (V/Q) scanning, spiral computerised tomography, pulmonary angiography and venous leg imaging] necessitate the use of these tests in series and in combination with clinical pretest probability assessment and D-dimer in diagnostic management algorithms. These algorithms permit safe diagnostic management of patients with suspected PE while limiting invasiveness, inaccessibility and expense.

Key Words: Pulmonary embolism; Diagnosis; Ventilation–perfusion lung scan; Spiral CT; Angiography; D-dimer; Clinical probability; Prognosis; Ultrasound; Deep vein thrombosis

Corresponding author: Dr. Philip Wells, Suite 453, 737 Parkdale Avenue, Ottawa, Ontario, Canada K1Y 1J8. Tel.: +1 (613) 761 4127; Fax: +1 (613) 761 4840;
E-mail: <pwells@ottawahospital.on.ca>.

Pulmonary embolism (PE) is the third leading cause of cardiovascular mortality in North America with an age- and sex-adjusted estimated incidence rate of 21–69 per 100,000 per year in population-based studies [1–3]. PE is also responsible for 5–10% of all in-hospital deaths [3–5]. PE is an important diagnosis to establish, given that undiagnosed PE has a hospital mortality rate as high as 30%, which falls to a near 8% if diagnosed and treated appropriately [5–7].

The diagnosis of PE remains one of the most difficult problems confronting clinicians. PE is considered in the differential diagnosis of many clinical presentations, including chest pain, hemoptysis and dyspnea, and in a wide variety of clinical settings, such as emergency departments, obstetrical units, surgical wards and intensive care units. Yet, less than 35% of patients suspected of having PE actually have PE [8–10]. Therefore, many patients without PE are needlessly hospitalised and anticoagulated while awaiting confirmatory testing. Furthermore, many patients suspected of having PE in smaller centres without this diagnostic technology are transferred to larger centres. In larger centres, ventilation–perfusion (V/Q) scans, noninvasive leg studies and pulmonary angiograms are generally only available during weekdays and daytime hours, complicating the diagnostic approach for patients with suspected PE seen after hours in these centres. Given the high mortality of untreated PE, timely diagnostic testing must be performed to enable the initiation of antithrombotic therapy for patients proven to have this condition while avoiding the risks of anticoagulation for patients in whom this diagnosis is excluded [11].

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In this review, we will explore the diagnostic value of the clinical assessment, D-dimer testing, V/Q lung scanning, venous ultrasound imaging of the legs, pulmonary angiography and spiral CT in patients with suspected PE. We will then conclude by suggesting diagnostic management approaches for patients with suspected PE.

1. The Clinical Assessment of Suspected PE

The clinical assessment for PE will be considered first by examining the diagnostic value of the individual components (i.e., symptoms, signs, risk factors, laboratory tests, electrocardiogram (ECG), arterial blood gas and chest X-ray) and then considering the diagnostic value of the overall clinical assessment (i.e., the clinician's overall diagnostic impression).

Four authors have reported on the sensitivity and specificity of individual signs and symptoms [12–16]. Patient age is consistently a statistically significant univariate predictor for PE across these studies. This is consistent with population-based epidemiological data demonstrating an increased incidence of PE with age [1]. Patient's sex does not appear to be predictive. Individual presenting symptoms do not reliably differentiate between patients with and without PE. The exceptions in individual studies include pleuritic chest pain and sudden dyspnea. Leg symptoms are consistently more likely in patients with PE but in no study did this reach statistical significance. Interestingly, hemoptysis is a rare presenting symptom in suspected PE, but in many studies, hemoptysis is consistently more common in patients with PE. Risk factors for venous thromboembolic disease are well characterized in the literature [17]. In a review of 1231 patients treated for confirmed venous thromboembolic disease, one or more risk factors was present in over 96% of patients. Furthermore, in the PIOPED study, the presence of one or more risk factors was more common in patients with PE as opposed to those without PE. In patients with suspected PE, the only risk factors, which are consistently present more often in patients who are ultimately confirmed to have PE, are immobilization, recent surgery, malignancy and previous venous thromboembolic disease. However, only immobilization and recent surgery reached statistical significance. Patients with PE are more likely to be tachypneic and tachycardic than patients without PE but these differences were only statistically significantly different in one study. In studies reported to date, there appears to be no difference in blood pressures, the presence of a pleural rub on auscultation or temperatures in patients with confirmed and suspected PE. One commonly held misconception is that the presence of chest wall tenderness in patients with pleuritic chest pain excludes PE [18]. The presence of a fourth heart sound (S4), loud second pulmonary heart sound (P2) and inspiratory crackles on chest auscultation were more common in patients with PE than patients without PE in one study [14].

A variety of ECG changes have been suggested to have diagnostic value in patients with suspected PE [13,14,19,20]. However, the majority of these investigations have only studied patients with confirmed PE. Few authors have reported on the prevalence of ECG changes in patients with suspected PE. The diagnostic value of a test can only be determined by applying the test in patients with suspected disease and then determining if the test is predictive of outcome. Further, previous investigations examining the diagnostic value of the ECG in suspected PE have been limited by patient selection (critical care patients only) [21,22] or not comparing the diagnostic value of the ECG to an appropriate reference standard (perfusion scans only) [22]. In a study of unselected patients with suspected PE with gold standard outcome measures, we found that tachycardia and incomplete right bundle branch block were significantly more frequent in PE patients than non-PE patients. However, these ECG changes were only marginally more frequently observed in PE patients or rarely observed, thus limiting their diagnostic utility [23]. One commonly held misconception is that a normal A-a gradient excludes PE [24] despite reports to the contrary [25]. Two authors have proposed prediction rules based on arterial blood gas but these rules could not be validated in subsequent studies [25,26]. Recently, Egermayer et al. [28] showed that a negative D-dimer, a paO_2 of ≥ 80 mmHg and a respiratory rate less

than 20, also had a negative predictive value of 100% in patients with suspected PE. In our study population, we were only able to demonstrate a negative predictive value of 95% with this rule [27,28]. In summary, ABGs should not be ordered to rule in or rule out PE.

In PIOPED, the most sensitive chest X-ray change was atelectasis or parenchymal abnormality and had a sensitivity of only 68% [14]. In another investigation, chest X-rays in patients with suspected PE were interpreted by radiologists who agreed on the presence of PE in only one-third of patients and in only one-third of these was the diagnosis correct [29].

Despite the limitations of the individual clinical predictors described above, in the early 1990s, the PIOPED investigators demonstrated that indeed the overall clinical assessment (i.e., clinicians overall diagnostic impression) was of utility in diagnostic management. In the PIOPED study, experienced clinicians were able to separate a cohort of patients with suspected PE into high-, moderate- and low-probability groups using clinical assessment alone [8]. More recently, Perrier et al. [30] were also able to stratify patients into different risk categories using clinical assessment alone. In both of these studies, patients were stratified into risk categories using the clinical judgement of the individual clinicians based on overall diagnostic impression alone (i.e., not using a predefined clinical decision tool).

We recently published our experience with an explicit clinical model to determine pretest probability for PE using clinical findings, ECG and chest X-ray [9]. The explicit clinical model (Fig. 1) consisted of consideration of whether the patient's clinical presentation based on symptoms, signs and risk factors was typical for PE and whether there was an alternative diagnosis at least as likely as PE to account for their symptoms. In this study, over 1200 inpatients and outpatients with suspected PE were evaluated by clinicians and separated into low-, moderate-, and high-probability subgroups using this explicit clinical model. The prevalence of PE in the low-, moderate- and high-probability subgroups were 3%, 28% and 78%, respectively. In an attempt to simplify the explicit clinical model, we subsequently performed a logistic regression on the clinical

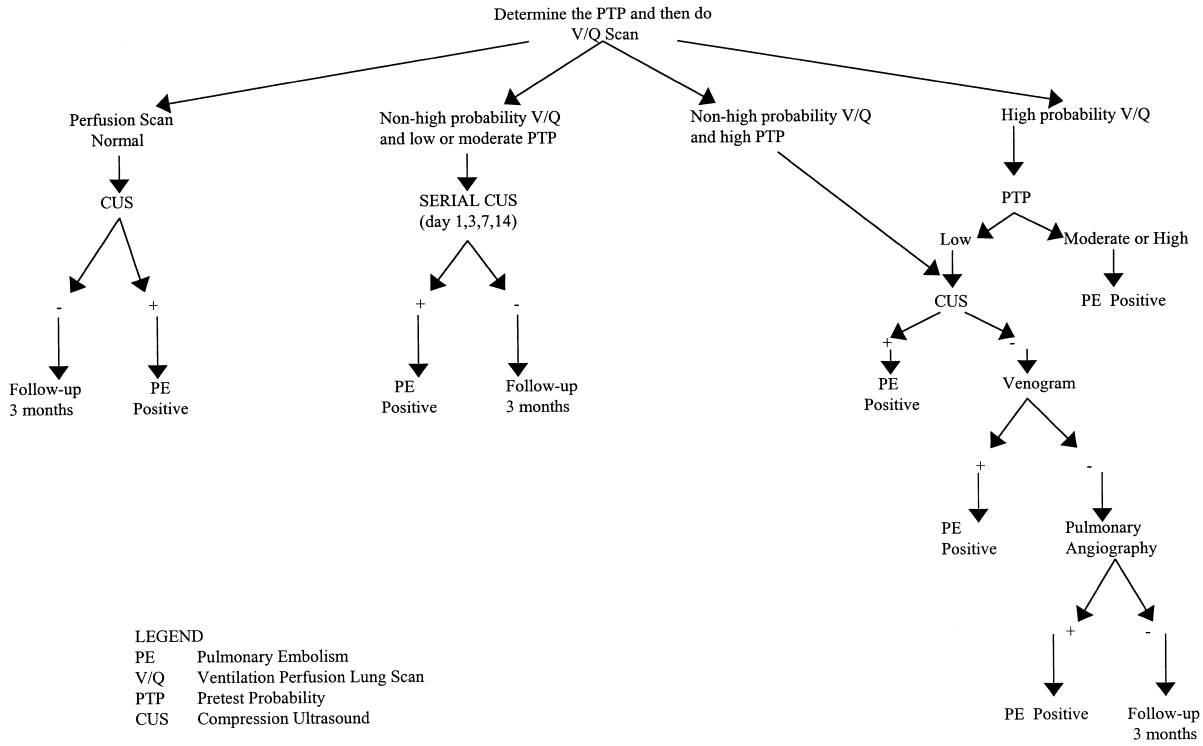

Fig. 1. Diagnostic strategy used in patients with suspected PE.

data collected in the above study to derive a simplified explicit clinical model (see Table 1) [31]. The interim analysis of validation trial of the simplified explicit clinical model has been published in abstract. Preliminary results have demonstrated that the simplified explicit clinical model can separate patients into low-, moderate- and high-risk subgroups although it appears that the emergency physicians have a lower threshold for suspecting PE, so the overall PE rate was low in the validation study [32]. More recently, Miniati et al. [33] reported the benefits of clinical assessment. Their combination of clinical predictors (symptoms, ECG findings and chest X-ray findings) had a negative predictive value of 94% and PE could be excluded in 42% of patients in their validation set.

2. V/Q Lung Scanning

For over 30 years, V/Q lung scanning has been used as the imaging procedure of choice for the evaluation of patients with suspected PE. The accuracy of lung scanning has been evaluated in two studies that used pulmonary angiography as the gold standard [8,10]. These studies demonstrated that a normal perfusion lung scan essentially excludes the diagnosis of PE and a high-probability lung scan has an 85–90% positive predictive value for PE. However, using pulmonary angiography as the gold standard, two studies have demonstrated that between 45% and 66% of high-probability lung scans are falsely positive when a skilled clinician deemed the patient's pretest probability for PE low [8,10]. Similarly, if the clinical pretest probability is high but the scan is nondiagnostic, further investigation, preferably angiography, is necessary to exclude or confirm the diagnosis of PE. A further limitation of V/Q lung scanning is that most lung scans fit into a nondiagnostic category (neither normal nor high probability) in which the incidence of PE varies from 10% to 30%. Criteria have been developed by the PIOPED investigators to distinguish moderate-probability (termed intermediate, incidence of PE 30%) from lower-probability (termed low, incidence of PE 15%) scans. However, the designation of a low-probability lung scan has been criticized because of the interpretation by some clinicians that ''low probability'' means ''no probability,'' and on this basis, anticoagulant therapy has been withheld inappropriately in some patients with serious consequences [34,35]. Therefore, we prefer to use the designation of nondiagnostic for all scan results that are neither normal nor high probability. Further testing is required to exclude the diagnosis of PE in these patients.

Table 1. Variables used to determine patient pretest probability for PE

• Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins)	3.0 points
• PE as or more likely than an alternative diagnosis	3.0 points
• Heart rate greater than 100	1.5 points
• Immobilization or surgery in the previous 4 weeks	1.5 points
• Previous DVT/PE	1.5 points
• Hemoptysis	1.0 points
• Malignancy (on treatment, treated in the last 6 months or palliative)	1.0 points

Low probability: <2.0; moderate probability: 2.0–6.0; high probability: >6.0.

3. Pulmonary Angiography

The presence or absence of an intravascular filling defect on pulmonary angiography respectively confirms or refutes PE [8]. Despite maintaining the gold standard test for PE, many clinicians choose not to pursue pulmonary angiography in patients with suspected PE [36–39]. The reasons clinicians do not use the gold standard include (1) a fear of the mortality associated with pulmonary angiography, (2) its limited availability after hours and in smaller centres and (3) the expense and expertise required to perform pulmonary angiography. Although the procedure is usually well tolerated, arrhythmia, hypotension and other adverse reactions to contrast dye may be observed. The best data on morbidity and mortality, death in 0.5% and major non-

fatal morbidity in 1.0%, were determined prior to the widespread use of nonionic low-osmolar contrast [40]. Further, 3/5 of deaths were in patients with poor cardiopulmonary reserve prior to angiography so the procedure is likely safer in patients without poor cardiopulmonary reserve. However, a more recent single institution study had no fatalities in 1400 patients and major complications in 0.3% [41]. The above limitations are likely the reasons why a significant number of patients with nondiagnostic V/Q scans are managed inappropriately [36]. Further, pulmonary angiography is also an imperfect test. A patient with a normal pulmonary angiogram can expect a 2.2% (95% CI of 0.3–8.0%) venous thromboembolic event rate at 1-year follow-up [10]. Thus, although we are not suggesting that performing angiography in patients with suspected PE is an incorrect approach, the limitations must be appreciated.

4. Venous Ultrasound Imaging Studies of the Legs

The greatest utility for venous ultrasound imaging in patients with suspected PE is in patients with high pretest probability for PE, patients with both risk factors for PE and with signs and symptoms of DVT. In these groups, ultrasound will be positive in 46% and 15%, respectively [9,42]. This eliminates the need for pulmonary angiography in many patients with these characteristics. Although there is evidence that venous ultrasound imaging should not be the first diagnostic test in patients with suspected PE, since only 15% of all patients will have evidence of deep vein thrombosis on ultrasonography, this does not negate the utility of this test [43]. Nonetheless, we have demonstrated that in patients with non-high-probability V/Q scans and initial normal ultrasonography, the performance of three additional ultrasonography tests over a 2-week period (serial ultrasound testing) can be used to safely exclude the diagnosis of PE [44]. The limitations of this approach are that it is both inconvenient and cost-ineffective since relatively few patients undergoing serial testing will actually have PE.

5. D-dimer for Diagnosis of Venous Thromboembolism

D-dimer is a degradation product of a cross-linked fibrin blood clot. Levels of D-dimer are typically elevated in patients with acute venous thromboembolism. D-dimer levels may also be increased in a variety of nonthrombotic disorders including recent major surgery, hemorrhage, trauma, malignancy or sepsis. Therefore, D-dimer assays are, in general, sensitive but nonspecific markers for venous thromboembolism. Many different D-dimer assays have been evaluated for the diagnosis of venous thromboembolism and the accuracy of these tests vary. The most sensitive D-dimer tests are the enzyme-linked immunosorbent assays (ELISA). Until recently, ELISA D-dimer assays were performed on microplate readers, making the assay expensive, time-consuming and not practical to be performed in most centres as an urgent diagnostic test. However, semiquantitative and a rapid fluorescence quantitative ELISA D-dimer assays have been developed which maintain the high sensitivity of the test and have lowered the test turn around time to less than 1 h [45]. Two other D-dimer assay methods that have been evaluated as diagnostic markers for PE are whole blood agglutination assay (SimpliRED) and latex agglutination plasma assays [46]. These assays have the advantages of being simple to perform, having a rapid turn around time and being inexpensive. They are less sensitive but more specific than the ELISA assay. As a result of these diagnostic characteristics, a positive D-dimer result is not useful to ''rule in'' the diagnosis of venous thromboembolism. Rather, the potential value is for a negative test result to exclude the diagnosis [47,48]. Some reports suggest the rapid ELISA tests have 100% sensitivity. However, there is some risk in assuming that ELISA or rapid ELISA D-dimer tests have 100% sensitivity since very few tests will consistently have such a sensitivity. One recent study illustrates this. The VIDAS D-dimer had a sensitivity of only 90% in this study of patients who underwent pulmonary angiography, but most of the false negative results were in patients with subsegmental PE [49]. The negative predictive value of the D-dimer increases proportionately depending upon the sensitivity

of the assay but will be inversely related to the prevalence of venous thromboembolism in the population under study. Therefore, the specificity of the particular D-dimer assay and the population under study influence the utility of the assay to exclude the diagnosis of venous thromboembolism. For instance, use of the less-specific ELISA assays when testing ill, hospitalised patients would be predicted to be of lower value due to the expected high false-positive rates that would be observed [45]. Conversely, the higher specificity assays may be more useful as recently demonstrated. In this study of hospitalised medical and surgical patients, the SimpliRED D-dimer was negative in 47% of the patients and the negative predictive value was 100%. In general, however, the SimpliRED and other assays with lower sensitivity than ELISA tests should only be considered as an exclusionary test in patient populations identified to have a lower prevalence of venous thromboembolism or in conjunction with other diagnostic [50]. This was demonstrated in a recent study evaluating the SimpliRED D-dimer assay in a cohort of 1177 inpatients and outpatients with suspected PE [47]. The D-dimer assay had a sensitivity of 85%, a specificity of 68% and a negative predictive value of 96%. The negative predictive value of the D-dimer test varied depending upon clinical probability from 99.0% (95% CI of 97.8–99.7%) in patients at low pretest probability to 87.9% (95% CI of 81.9–92.4%) for moderate-probability patients to 64.3% (95% CI of 35.1–87.2%) for high-probability patients.

6. Spiral CT Angiography

Over the past decade, contrast-enhanced spiral CT has emerged as a new noninvasive imaging modality for the investigation of patients with suspected PE [51,52]. Spiral CT has made it possible to directly visualize segmental and some subsegmental arteries using a single bolus of contrast while advancing a patient through the X-ray beam. Technical drawbacks of spiral CT include that it requires contrast, greater radiation exposure than with V/Q scanning and a cooperative patient since evaluation of segmental pulmonary arteries may be suboptimal due to motion artifact if patients are unable to hold their breath for 15–25 s. In addition to being a diagnostic test, spiral CT may identify alternative causes for symptoms in patients with suspected PE. However, most parenchymal and pleural changes, including wedge-shaped pleural opacities, are found in patients with and without PE [53].

A pooled analysis of five comparative studies using pulmonary angiography as the gold standard determined the overall sensitivity and specificity of spiral CT for the diagnosis of PE to be 72% (95% CI of 59–83%) and 95% (95% CI of 89–98%), respectively [54]. However, for central PE, those involving the main pulmonary arteries and their segmental branches, the sensitivity of CT increased to 94% (95% CI of 86–98%) and the specificity remained high (94%; 95% CI of 88–98%). Two more recent systematic reviews have further questioned the validity of studies evaluating the accuracy of spiral CT [54,55]. Both reviews raised concerns about the reported wide variation in the overall sensitivity of spiral CT between studies (from 53% to 100%) and of the failure of these accuracy studies to follow basic methodological principles for evaluating a diagnostic test.

Three small studies have directly compared spiral CT with V/Q scanning in cohorts of patients with suspected PE. These studies, using pulmonary angiography as the gold standard, have consistently favored spiral CT as the more accurate imaging procedure. Mayo et al. [52] found in 12 patients in whom there was discordance between the spiral CT and the V/Q scan result, spiral CT demonstrating the correct diagnosis in 92%. Garg et al. [56] demonstrated in 18 of 21 (86%) of patients with intermediate probability V/Q scans that spiral CT concurred with pulmonary angiography findings. Cross [57] performed a randomized cross-over study and found none of 39 patients with negative spiral CT had a high-probability V/Q result. However, 2/20 (10%) patients with intermediate probability V/Q scans had PE detected by spiral CT.

Despite the concerns raised in recent publications about the uncertain sensitivity of spiral CT and the lack of studies evaluating the safety of relying on spiral CT to exclude the diagnosis of PE, its use has been strongly supported in editorials and reviews in the radiology literature [58–

61]. In addition, in a recent survey we performed in Canadian hospital radiology departments, we found that of the 100 responding hospitals with greater than 200 beds, 91% are performing spiral CT for the diagnosis of PE compared with 97% performing V/Q scanning. Many of the responding radiology department heads indicated that spiral CT was the preferred initial test for PE by both the clinicians and radiologists in their hospitals (unpublished data).

Only one study has compared the relative cost-effectiveness of spiral CT and V/Q scanning for the evaluation of patients with suspected PE. It reported that a spiral CT-based diagnosis algorithm was the most cost-effective regimen (US$16,000 per life year saved) vs. V/Q scanning (US$27,000 per life year saved) [62]. However, this study based outcome estimates on a literature review, which assumed spiral CT was highly sensitive (97%), costs were in Dutch currency and in their health system and the data came from 1996. It is unclear how costs would compare in other countries and how the analysis would change if the lower sensitivities found in the pooled validity studies (see above) had been employed.

Despite concerns about the uncertain sensitivity of spiral CT, several features make it more attractive than V/Q scanning as an imaging procedure for patients with suspected PE. First, the specificity of the test is very high (90–100%, compared to V/Q scanning, for which an abnormal result has a specificity of about 10%). The three systematic reviews have verified that a positive spiral CT is likely sufficient for ruling in a diagnosis of PE. Second, the sensitivity of spiral CT is high for large central pulmonary emboli (83–100% in the systematic reviews), those that are most likely to be clinically important. The sensitivity of spiral CT exceeds that of a high-probability lung scan, which was only about 45% in the PIOPED study. Most of the discrepancy in reported sensitivities of spiral CT involve the categorization of small, subsegmental pulmonary emboli, which account for 6–36% of all pulmonary emboli and are of uncertain clinical significance. Although such small emboli in themselves may carry a low risk of serious complications, they may be a harbinger for subsequent thromboembolic complications. Third, spiral CT maybe useful for directly identifying alternative causes for a patient's presentation, as opposed to V/Q scanning, which rarely assists in this regard. Fourth, interobserver agreement in interpreting scan results is higher for spiral CT than V/Q scanning [52,63].

Given that spiral CT appears to be both more sensitive and specific (at least for central PE) than V/Q scanning, it is likely that safe diagnostic management approaches will be developed with spiral CT as the initial diagnostic test. However, the only management study to date has not been convincing. Ferretti et al. [64] examined the impact of managing patients with intermediate probability lung scans and normal bilateral venous ultrasound using spiral CT. However, in the 3-month follow-up period, 5% of the 129 patients developed symptomatic venous thromboembolic complications, three with pulmonary emboli, including one fatality and three with deep vein thrombosis. Further research is required to determine whether D-dimer or clinical assessment may be used as adjunctive tests in patients with normal spiral CT investigations who have normal venous ultrasound imaging studies to increase the safety of spiral CT-based approaches.

In summary, spiral CT appears to be a promising tool in the diagnostic management of suspected PE. However, large management trials are required before concluding that a negative spiral CT safely excludes PE. Further, adequately powered randomized trials are required to determine whether diagnostic management approaches based on spiral CT should replace the current standard (i.e., diagnostic management approaches based on V/Q scanning).

7. Diagnostic Management of Patients with Suspected PE

We will describe three approaches for the diagnosis of PE using V/Q lung scanning as the primary diagnostic test.

In the first approach (see Fig. 1), patients should have pretest probability assigned by clinical assessment (by overall diagnostic impression or an explicit clinical model) and then V/Q scan performed. A normal scan safely excludes the

diagnosis of PE. If the lung scan result is high probability, then the diagnosis of PE can be made with over 90% certainty as long as the clinical suspicion for PE is moderate or high. If the clinical likelihood of PE is low, patients with high-probability lung scans should undergo confirmatory testing with either pulmonary angiography or spiral CT. If the lung scan is non-high-probability, additional diagnostic testing is required to confirm or exclude the diagnosis of PE. Historically, it has been recommended that patients with non-high-probability lung scans should undergo pulmonary angiography. Although this is an effective way to confirm or exclude PE, as discussed previously, this approach is not practical in many centers and has other limitations. In recent years, much attention has focused on the use of noninvasive tests for deep vein thrombosis in patients with suspected PE who have non-high-probability lung scans. The rationale for this approach is that the current therapeutic management of deep vein thrombosis and PE is similar. If noninvasive testing confirms the presence of deep vein thrombosis, then appropriate antithrombotic therapy can be initiated without the need to conclusively demonstrate by angiography whether PE is present or not. On the other hand, if noninvasive testing for proximal deep vein thrombosis is negative, then it would be reasonable to withhold antithrombotic therapy because such patients would potentially be at relatively low risk for additional pulmonary emboli (Fig. 1). The safety of using serial ultrasound imaging was recently demonstrated in a study by our group [9]. Patients at low or moderate clinical pretest probability for PE who had a non-high-probability lung scan and an initial negative ultrasound could be safely followed with serial ultrasonography without the need to institute anticoagulant therapy or perform pulmonary angiography. Those 665 patients who had two or three negative ultrasounds performed over a 2-week period following their initial evaluation had no greater risk (0.5%, 95% CI of 0.1–1.3%) of developing venous thromboembolic complications over a 3-month period than those 334 patients whose initial lung scan was normal (0.6%, 95% CI of 0.1–1.8%).

An alternative approach for the management of patients with non-high-probability lung scans is to incorporate clinical probability and D-dimer into the diagnostic management algorithm. Perrier et al. [30] studied 444 patients with suspected PE presenting at the emergency department or outpatient clinics. First, the clinical probability of PE was determined using the principles we described (i.e., looking at risk factors, signs and symptoms and alternative diagnosis) but not using an explicit model. D-dimer was next and, if negative, PE as considered was excluded. Patients with positive D-dimer then had venous ultrasound imaging and, if abnormal, PE was diagnosed. If ultrasound was normal, V/Q scanning was performed. If the V/Q scan was normal or near normal, PE was excluded. However, if high probability, PE was diagnosed. The remaining patients had non-high-probability V/Q scans. If the clinical probability was low, then PE was excluded and otherwise pulmonary angiography was performed. Only 11% of patients required

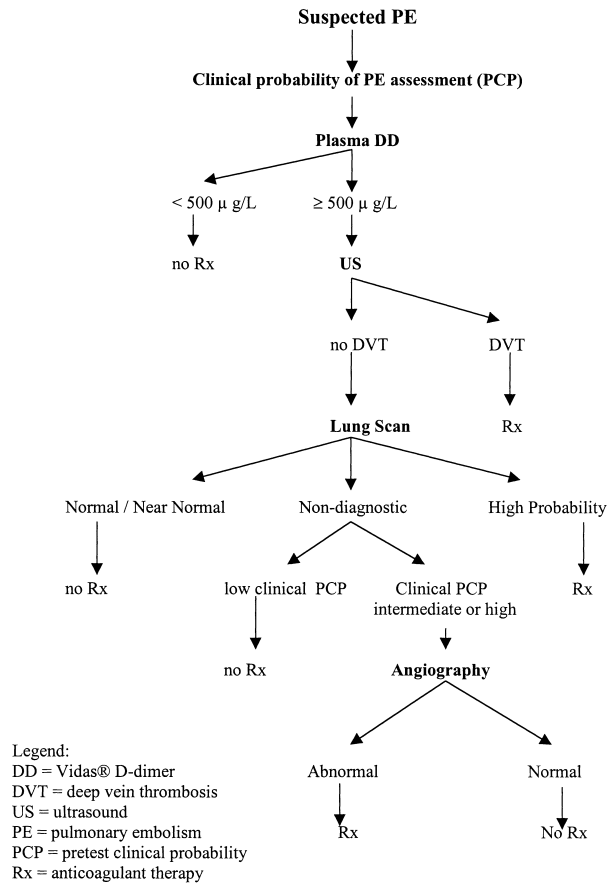

Fig. 2. Diagnostic algorithm in patients with suspected PE that utilizes D-dimer as first diagnostic test.

angiography and follow-up event rates were low (Fig. 2).

In the third approach, physicians first used our clinical model to categorize patients' pretest probabilities as low, moderate or high. D-dimer (SimpliRED) was then performed. Patients with low pretest probability and a negative D-dimer had no further tests and were considered to have a diagnosis of PE excluded. All other patients underwent V/Q lung scans and bilateral deep vein ultrasound if the V/Q scan was nondiagnostic. Further testing by serial ultrasound or angiography depended on the pretest probability and the lung scan results as outlined in Fig. 3. Patients were diagnosed with PE if they had high-probability V/Q scan, abnormal ultrasound, abnormal pulmonary angiography or a venous thromboembolic event within the 3-month follow-up period. All others were considered to have PE excluded and did not receive anticoagulant therapy. This strategy resulted in very few patients (<1%) with venous thromboembolic events during follow-up. Incorporation of the D-dimer into the diagnostic algorithm with pretest probability significantly and safely decreased the need for diagnostic tests [65].

Improvements in care by using diagnostic management algorithms have recently been confirmed outside of the research setting by Berghout et al. [66]. Before the use of an algorithm, 55% of patients with abnormal perfusion scans were

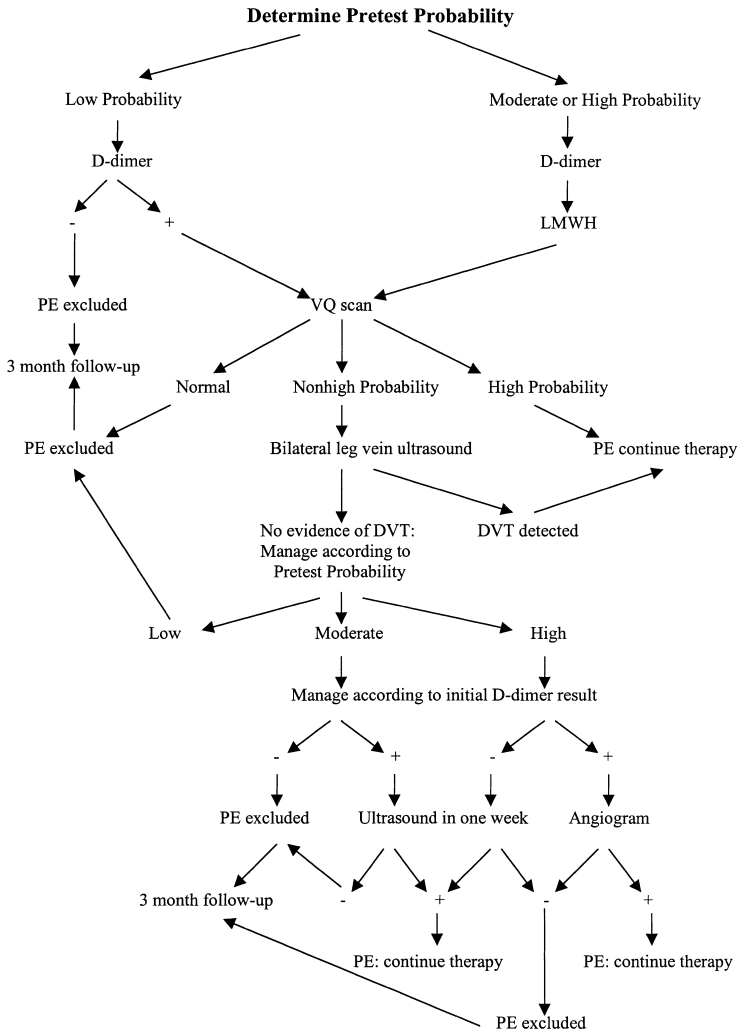

Fig. 3. Algorithm combining D-dimer and clinical probability for patients with suspected PE.

treated with anticoagulants without a confirmed diagnosis, and only 11% of patients had adequate confirmation of PE when the scan was abnormal. These rates decreased to 13% and increased to 59%, respectively, after the use of a diagnostic management algorithm. Further improvement occurred after another year of observation.

8. The Prognostic Significance of Diagnostic Tests

It is logical to assume that PE and deep vein thrombosis are different manifestations of the same disease since up to 80% of patients with PE will have deep vein thrombosis demonstrated by venography and a series of six studies demonstrated that 48% of patients with deep vein thrombosis have high-probability V/Q scans despite a lack of symptoms in the majority. However, Douketis et al. [67] demonstrated that the probability of death is higher in patients who present with symptoms of PE rather than just deep vein thrombosis. Another investigator demonstrated similar findings [68]. Furthermore, it has been suggested that right ventricular hypokinesis detected by echocardiography at the time of diagnosis portends a higher risk of death [69]. Others reported similar findings [70,71]. Recently, Giannitsis et al. [72] identified cardiac troponin T (cTnT) as an independent predictor of 30-day mortality. They have suggested that this is due to an acute increase in RV afterload and consequent severe myocardial ischemia, the latter not due to coronary artery disease since most of the patients had insignificant coronary disease on angiography. Unfortunately, it is not clear that identifying patients at high risk will effect outcome and all these studies have limitations. Nonetheless, in patients with preexisting cardiopulmonary disease or those with any degree of hemodynamic instability, it is probably worth performing echocardiography to assess right ventricular function to help select those patients that warrant close observation. These patients may be at higher risk for outpatient therapy and it is possible, but by no means yet demonstrated, that these patients may benefit from more aggressive therapy such as thrombolytics or inferior vena caval filters.

9. Summary and Conclusions

Recent advances in the management of patients with suspected PE have both improved diagnostic accuracy, as well as made management algorithms safer and more accessible. Ongoing clinical trials are evaluating whether these diagnostic processes can be made even simpler and less expensive. Attempts are being made to identify very low-risk patients with suspected PE in whom imaging procedures can be avoided altogether. Diagnostic procedures for PE continue to be refined and modalities such as magnetic resonance imaging and spiral CT have the potential to further increase the accuracy and safety of the diagnostic management of suspected PE.

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