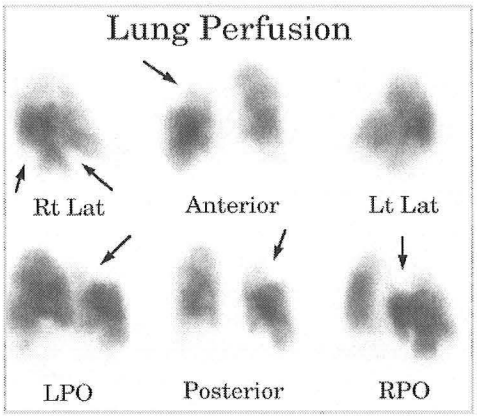

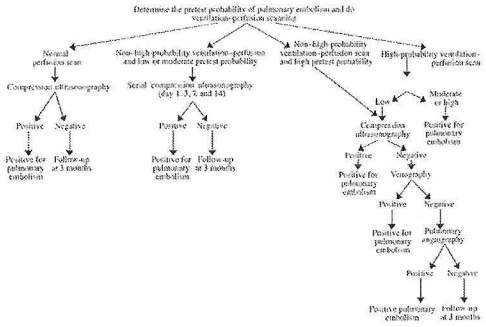

Non-invasive Strategies for the Diagnosis of Pulmonary Embolism Their Role and Limitations

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Internal Medicine Grand Rounds
University of Texas Southwestern Medical Center
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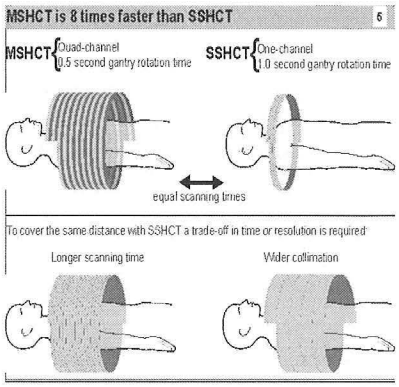

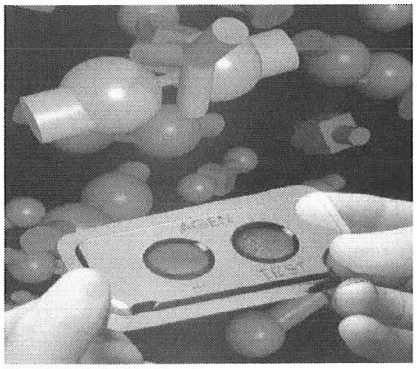

This is to acknowledge that Dr. Guna Raj has not disclosed any financial interests or other relationships with commercial concerns related directly to this program. Dr. Raj will not be discussing off-label uses in her presentation.

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Interests
Clinical Issues Related to Anticoagulant Therapy
Primary Care

Case Presentation

Case 1.

A 34 y/o man was admitted with cough, hemoptysis, and shortness of breath with exertion and at rest for 3 days. He denied chest pain, fever or recent travel. Past medical history was significant for 2-3 visits to the emergency department with brief episodes of cough and streaky hemoptysis that were diagnosed as acute bronchitis. Pulmonary embolism (PE) was considered about a year ago during one of these episodes and ruled out after a ventilation-perfusion lung scan (V/Q) was reported as "Low probability for PE". His initial examination was reported as unremarkable but because of clinical suspicion for PE the patient was started on heparin and a spiral computed tomography angiogram (SCTA) was ordered which was reported to show no evidence of pulmonary emboli. A small left sided pleural effusion and consolidation within the posterobasal segment of the left lower lobe were noted. The patient was started on antibiotics for possible community acquired pneumonia. At rounds the next morning the attending physician noted elevated jugular venous pressure (JVP), prominent superficial veins on the left anterior chest wall and a loud P_2. A reevaluation of SCTA was requested. Another experienced radiologist reviewed the CT with para-axial, para-coronal, and para-sagittal reconstruction of the images acquired the previous day. Subsegmental emboli were revealed in bilateral lower lobes on these images. A duplex scan of the left upper extremity also showed thrombus in the internal jugular vein and the proximal left subclavian vein.

Case 2.

A 73 year old man with chronic obstructive pulmonary disease (COPD), type 2 diabetes mellitus, high blood pressure and chronic renal insufficiency with a creatinine of 1.8-2.0mg/dL was admitted with increasing shortness of breath for 2-3 weeks. He also reported chronic cough with some increase in sputum production during this period for which he had received a 10 day course of levofloxacin with clearing of sputum production but not the shortness of breath. He reported some left lower chest pain for 2 days. Exam revealed normal temperature, heart rate of 114 beats/minute, blood pressure 120/62mm Hg, oxygen saturation of 93-95% on 2L oxygen by nasal canula. He had trace ankle edema, JVP of 10cm, distant heart sounds, decreased breath sounds without wheezes or rales. Laboratory data showed a creatinine of 2.1mg/dL, glucose 132mmol/L, normal complete blood count, and cardiac enzymes. Room air arterial blood gas (ABG) showed pH of 7.41, PCO2 of 40 and PO2 of 49.7mm Hg compared to base line value on room air of 7.40/48/85 respectively in 2001. Electrocardiogram showed sinus tachycardia and chest radiograph showed a tubular heart shadow and prominent pulmonary vasculature.

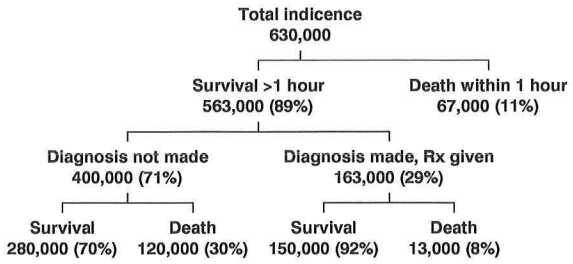
He was treated for COPD exacerbation with nebulized bronchodilators and steroids. A D-dimer test was positive. V/Q scan was performed which was read as low probability for PE. He was discharged home on antibiotics and a tapering dose of steroids. He was seen on follow-up 3 weeks later with continued dyspnea.

These two cases raise several questions. What was the significance of the low probability V/Q scan in the first case a year ago? Does he now have recurrent PE? What is the significance of the subsegmental PE seen on SCTA this time? Are they responsible for the signs of pulmonary hypertension? Is the thrombus in the upper extremity the source of his PE?

Was PE conclusively ruled out in the second patient? What is the significance of a positive d-dimer test? Should he have been investigated further, and how?

Pulmonary Embolism (PE) is a common cause of morbidity and mortality in this country (Figure 1). While exact numbers for the incidence of PE are difficult to come by, the estimated incidence of pulmonary embolism in the United States is about 600,000 cases a year, of which a third are fatal. About 67,000 die within one hour, before seeking adequate medical attention. Of the remaining 500,000 or so who survive long enough to seek medical attention the diagnosis is made in only about 30%. Thus PE is undiagnosed and untreated in the majority of patients (1).

Figure 1. Incidence of Pulmonary Embolism per Year in the United States



Prospective studies from the1990's indicate that in patients who are diagnosed and treated appropriately overall mortality is 15% at 3 months and 24% at 1 year. About half the deaths are attributed directly to PE and the other half to patients' underlying disease processes. Advanced age, cancer, congestive heart failure (CHF), COPD, systolic blood pressure < 90mm Hg or respiratory rate > 20/min at presentation and presence of right ventricular hypokinesis on echocardiogram are independently associated with increased mortality (Table 1) (2). Although a first episode is an uncommon cause of death in an otherwise healthy patient, it is associated with a high rate of recurrence, which is more likely to be fatal. Recurrent PE is diagnosed in 7-8% of patients and carries a much higher mortality rate of about 45% (2, 3). The risk of recurrence is highest in the first three months after an initial episode of PE. While treatment related major bleeding complications occur in almost 10% of patients, death is rarely attributed to treatment. Even though PE is a common event most patients are undiagnosed or untreated at the time of death. Prompt and accurate diagnosis is important to prevent mortality and avoid unnecessary treatment. There are many reasons for under-diagnosis; 1) pulmonary embolism may be clinically silent, 2) objective tests are required as the signs and symptoms of PE are neither sensitive nor specific (Table 2), 3) clinicians are reluctant to order pulmonary angiogram, the definitive gold standard test for diagnosis because of the invasive nature of the test and perceived risk, 4) lack of a reliable noninvasive diagnostic test. Efforts to decrease death and morbidity from PE should focus on increasing awareness of this disease and improving available diagnostic tests.

Table 1*
Factors Associated with Increased Mortality

Variable	Hazard Ratio (95% CI)
Age > 70 years	1.6 (1.1-2.3)
Cancer	2.3 (1.5-3.5)
Clinical CHF	2.4 (1.5-3.7)
COPD	1.8 (1.2-2.7)
Systolic BP <90 mm Hg	2.9 (1.7-5.0)
Respiratory rate > 20/min	2.0 (1.2-3.2)
Right ventricular failure	2.0 (1.3-2.9)

* ICOPER data

Table 2*
Presenting Symptoms and Signs

Dyspnea	82%
Chest pain	49%
Cough	20%
Syncope	14%
Hemoptysis	7%
Cardiac enlargement	36%
Pleural effusion	30%
Elevated hemidiaphragm	26%
Enlarged pulmonary artery	25%
Atelectasis	24%
Infiltrate	23%
RBBB	16%
Atrial fibrillation	14%

Diagnostic Tests for PE

Chest Radiograph: The following chest xray findings were observed in a prospective observational study of 2454 consecutive patients who had received a diagnosis of PE; cardiac enlargement (27%), no abnormality (24%), pleural effusion (23%), elevated hemidiaphragm (20%), pulmonary artery enlargement (19%), atelectasis (18%), and parenchymal pulmonary infiltrates (17%) (4). Other findings that have been reported in patients with PE include regional oligemia (Westermark's sign), pleural-based wedge shaped densities above the diaphragm (Hampton's hump), and sausage shaped enlargement of the right descending pulmonary artery (Palla's sign) (5).

Electrocardiogram: Sinus tachycardia and T wave inversion in the anterior chest leads (V1 to V3 or 4) are the most frequent electrocardiographic abnormalities reported in different series but they are neither sensitive nor specific. Prominent S wave in lead 1, and a Q wave and negative T wave in lead 3 (S1,Q3,T3 pattern) or a new complete or incomplete right bundle-branch block can be clues to diagnosis as well (6, 7).

Clinical examination, chest radiography and electrocardiogram findings, alone or in combination, raise the suspicion of PE but lack sensitivity and specificity for the diagnosis of PE and we have to rely on objective tests in most of these patients.

Pulmonary Angiography is the gold standard against which all other tests have been compared. This is an invasive test, requires the use of radio-contrast agent, and not always available or feasible in all patients. Procedure related major, non-fatal complications occur in 0.3-1% of patients. Fatal complications occurred in 0.5% of 1,111 procedures in one study, mostly in seriously ill patients (8-10). Nevertheless, physicians may settle for diagnostic uncertainties in their reluctance to consider invasive tests, as evidenced by one study from a large teaching hospital where 92% of patients with low probability ventilation/perfusion (V/Q) scan and 78% of patients with indeterminate scan had no further diagnostic tests. However, 20% and 35% of patients respectively in these two groups were treated with anticoagulants (11, 12).

Noninvasive tests for PE

Noninvasive strategies for diagnosis of PE utilize tests that indirectly detect presence of vascular obstruction and abnormal perfusion in the lungs by scintigraphy (ventilation-perfusion scan or V/Q scan), detect presence of thrombi in the deep veins of the lower extremities as a surrogate marker for PE, directly visualize thrombi in the pulmonary arteries by means of computed tomography (CT) scans or magnetic resonance imaging (MRI) or detect markers of clot formation and lysis in the blood. These tests have been used alone or in combination in different studies, all with the aim of avoiding misdiagnosis and minimizing the need for pulmonary angiography.

In evaluating diagnostic tests or strategies for a disease that has serious consequences if missed, certain minimum requirements should be fulfilled.
Comparison against a gold standard
Reliability in groups with different prevalence rates
Favorable outcome when treatment is withheld on the basis of a negative test (clinical management studies).

Ventilation-Perfusion Scans:

Hull and his colleagues from Canada are credited with being the first to prospectively evaluate the role of V/Q scan in the diagnosis of PE by performing V/Q scan, pulmonary angiography and venography in 139 consecutive patients with suspected PE and assigning diagnostic probabilities to different combinations of scan readings (13).

The role of V/Q scan was firmly established in a later landmark study commonly referred to as the PIOPED (Prospective Investigation of Pulmonary Embolism Diagnosis) study (9). Nine hundred and thirty one patients referred for a V/Q scan or pulmonary angiogram for a clinical suspicion of PE were enrolled in the study from 6 clinical centers in the US and had V/Q scan. Seven hundred and fifty-five of the 931 underwent pulmonary angiography as well. V/Q scan interpretation and categories were slightly different (Table 3) more complicated in PIOPED than in the Hull/McMaster study(Table 5).

Table 3. PIOPED Scan Interpretation Categories and Criteria

High Probability	**≥ 2 Large (≥ 75% of a segment) segmental perfusion defects without corresponding ventilation or CXR abnormalities or substantially larger than either matching ventilation or CXR abnormalities** **≥ 2 moderate (≥ 25% and ≤ 75% of a segment) segmental perfusion defects without matching ventilation or CXR abnormalities and 1 large mismatched segmental perfusion defect** **≥ 4 moderate segmental perfusion defects without ventilation or CXR abnormalities**
Intermediate Probability (Indeterminate)	**Not falling into normal, very-low, low-, or high-probability categories** **Borderline high or borderline low** **Difficult to categorize low or high**
Low Probability	**Nonsegmental perfusion defects** **Single moderate mismatched segmental perfusion defect with normal CXR** **Any perfusion defect with a substantially larter CXR abnormality** **Large or moderate segmental perfusion defects involving no more than 4 segments in 1 lung and no more than 3 segments in 1 lung region with matching ventilation defects either equal to or larger in size and CXR either normal or with abnormalities smaller than perfusion defects** **> 3 small segmental perfusion defects (≤ 25% of a segment) with a normal CXR**
Very Low Probability	**≤ 3 small segmental perfusion defects with a normal CXR**
Normal	**No perfusion defects present** **Perfusion outlines exactly the shape of the lungs as seen on CXR**

CXR – chest roentgenogram

PIOPED results revealed the following; almost all patients with PE had abnormal scans of high, intermediate or low probability but so did most patients without PE (sensitivity 98%, specificity 10%). Specificity of a high probability scan interpretation was 97% but sensitivity was 41%. The positive predictive value of high probability scan was 87% and that of the intermediate probability scan 30%, whereas the negative predictive value of a low probability scan was 86% and that of the normal/near normal scan 96%. Only 13% of all patients had a high probability scan and 14% had a normal scan. Combining clinical probability estimates with scan reading improved the diagnostic accuracy of the scan and the overall chance of reaching a correct diagnosis (Table 4). Agreement among scan readers in the study was excellent for high (95%), very-low-probability (92%) and normal (94%) scan categories. It was not as good for intermediate- and low-probability categories (75% and 70% respectively).

The results of PIOPED can be summarized as follows:
When clinical probability estimates and scan readings are concordant, PE can be diagnosed or excluded with a high degree of certainty. A low probability scan in a patient with low clinical probability excludes PE and a high probability scan in a patient with moderate or high clinical probability establishes a diagnosis of PE. When clinical probability and scan readings are discordant PE cannot be diagnosed or excluded. Intermediate probability scans are not helpful regardless of clinical probability estimate. Normal or near normal scan readings exclude a diagnosis of PE.

The very low rate of PE in patients with normal V/Q scan and the safety of withholding anticoagulation therapy in such patients have been confirmed in other studies (9,14,15).

Table 4. PIOPED Results: V/Q Scan and Pulmonary Embolism Status			
Scan Category	**Clinical Probability**		
	High	**Intermediate**	**Low**
	PE+/ Number of Patients (%)		
High	**28/29 (96)**	70/80 (88)	5/9 (56)
Intermediate	27/41 (66)	66/236 (28)	11/68 (16)
Low	6/15 (40)	30/191 (16)	**4/90 (4)**
Normal	0/5 (0)	4/62 (6)	1/61 (2)

The complex scan interpretation and categories used in PIOPED, low inter-observer agreement for the low and intermediate scan categories and the 12-14% prevalence of PE in patients with a low probability scan in this and other studies have led many to abandon the low and intermediate scan categories and use the Hull/McMaster interpretation of normal, high probability and non-high probability categories. Regardless of how scans are interpreted it is clear that twothirds of patients with suspected PE will have a nondiagnostic scan and will need additional testing.

Table 5. Hull / McMaster scan Interpretation Categories and Criteria	
Normal	no perfusion defect
High probability	1 ≥ segmental or greater perfusion defects with normal ventilation or ≥ 2 large subsegmental perfusion defects [>75% or a segment] with normal ventilation
Non-high probability	ventilation-perfusion defects that do not qualify as normal or high probability

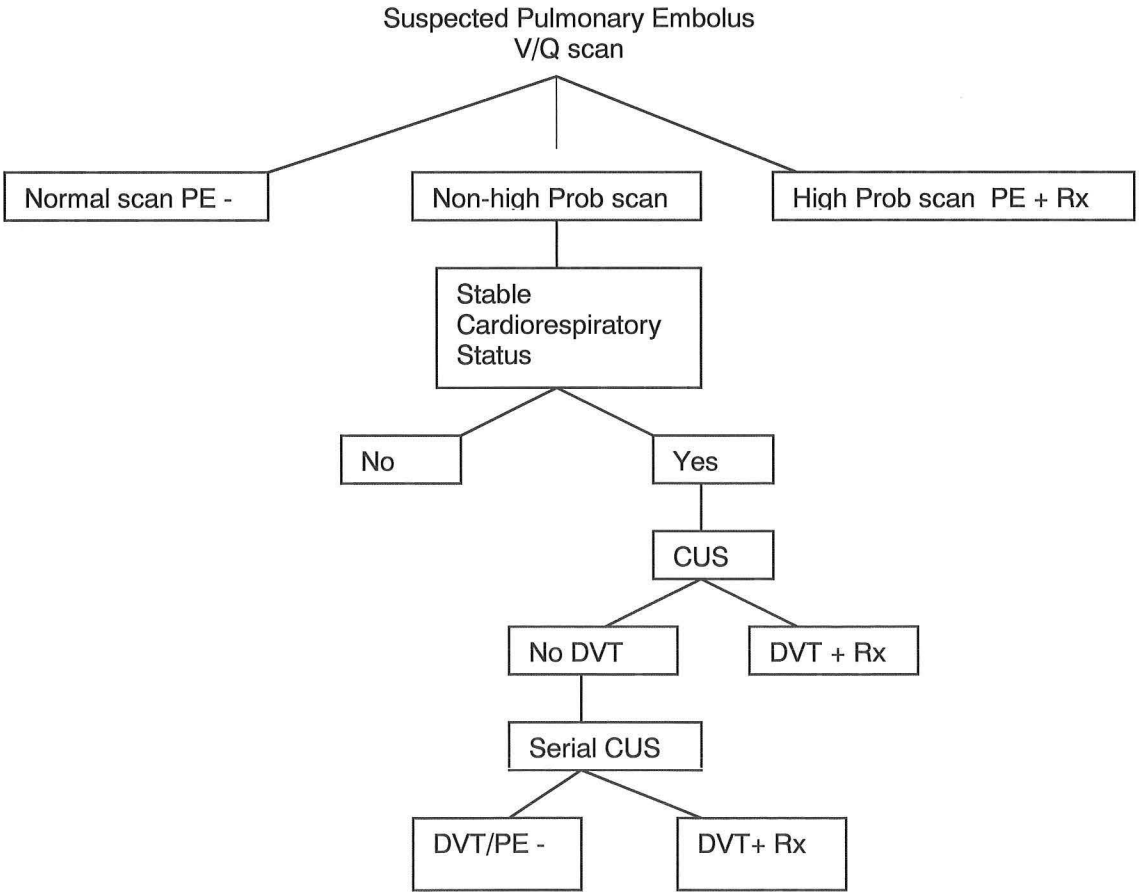
Tests for Deep Vein Thrombosis (DVT)

That PE is caused by thrombosis in the deep veins of the legs and pelvis has been known for some time as evidenced by this famous quote from a lecture given by Dr. Rudolf Virchow, the 19th century pathologist ".....the detachment of larger or smaller fragments from the end of the softening thrombus which are carried along by the current of blood and driven into remote vessels. This gives rise to the very frequent process upon which I have bestowed the name of *Embolia*". " Thus we see that, as a rule, all the thrombi from the periphery of the body produce secondary obstructions and metastatic deposits in the lung" (16). In more recent times objective tests have shown that a significant proportion of patients with proven PE have coexistent DVT. One study documented DVT in 70% of patients by ascending venography in all patients with angiographically proven PE while Impedence plethysmography (IPG) showed evidence of DVT in 51% of patients with high-probability V/Q scan and 19% of patients with indeterminate scans in the same study. (13). Compression ultrasonography (CUS) reveals DVT in about 30% of patients with high probability scan and 24% with non-high probability scan (17). Conversely, routine lung scans reveal silent PE in up to 50% of patients presenting with symptoms of DVT (18). Given this natural history of VTE and the need for prolonged anticoagulant treatment for both conditions, presence of DVT can be used as a surrogate for PE. With their high specificity noninvasive diagnostic tests for DVT have an important role in the evaluation and management of patients with suspected PE (19). Compression ultrasound of the lower extremities in patients with non-diagnostic V/Q scans can spare 15-20% of patients from further testing. While the sensitivity of noninvasive tests (IPG and CUS) for symptomatic DVT is very high it is not high enough for excluding DVT in asymptomatic patients or in patients with DVT limited to the calf veins (20). Patients with PE may have residual DVT confined to the calf veins only, which would explain the higher prevalence of DVT by ascending venography than by IPG or CUS in this group of patients. While thrombi limited to calf veins have a low risk of embolisation, up to 20% of such clots can extend proximally and potentially embolise. Repeating CUS in 7-10 days when initial CUS is negative will detect proximal DVT in the 20% of patients who may be at risk for proximal extension. (21-23).

The safety of withholding treatment when V/Q scan is nondiagnostic and serial objective tests for proximal vein thrombosis are negative has been prospectively investigated in several studies (Figure 2) (24, 25). In the largest of these studies 711 of 1564 (46%) consecutive patients presenting with signs and symptoms of PE and a nondiagnostic lung scan and adequate cardiopulmonary reserve (defined as absence of any of the following ; pulmonary edema, right ventricular failure, hypotension, syncope, acute tachyarrhythmias, abnormal spirometry of FEV_1 of <1.0, vital capacity of <1.5L, PO2 <50 or PCO2 >45 on room air) were investigated with serial CUS test on days 1, 3, 7 and 14. Eighty-four patients (11.8%) had DVT by noninvasive test, of which sixteen were detected on serial testing. Anticoagulation treatment was withheld in the remaining 627 patients with negative scan and normal serial CUS and followed for 3 months for evidence of symptomatic recurrence of DVT or PE. Twelve patients (1.9%, 95% CI 0.8 to 3.0%) developed objectively documented VTE on follow-up compared to 0.7 % (95% CI 0.02-1.3%) of 586 patients with normal lung scan ($p < 0.05$) suggesting that it was safe to withhold treatment in the cohort of patients with adequate cardiopulmonary reserve, non-diagnostic V/Q scan and normal serial test for DVT.

This noninvasive strategy had a negative predictive value (NPV) of 98%. Further invasive testing was avoided in 40% of patients with suspected PE. Applying this strategy to patients with inadequate cardiopulmonary reserve has not been tested and may not be safe. Such patients are at high risk of mortality with recurrent PE, and an undiagnosed PE may be the cause of poor cardio-respiratory reserve at presentation.

Figure 2. Noninvasive Strategy for the Treatment of Patients with Suspected PE



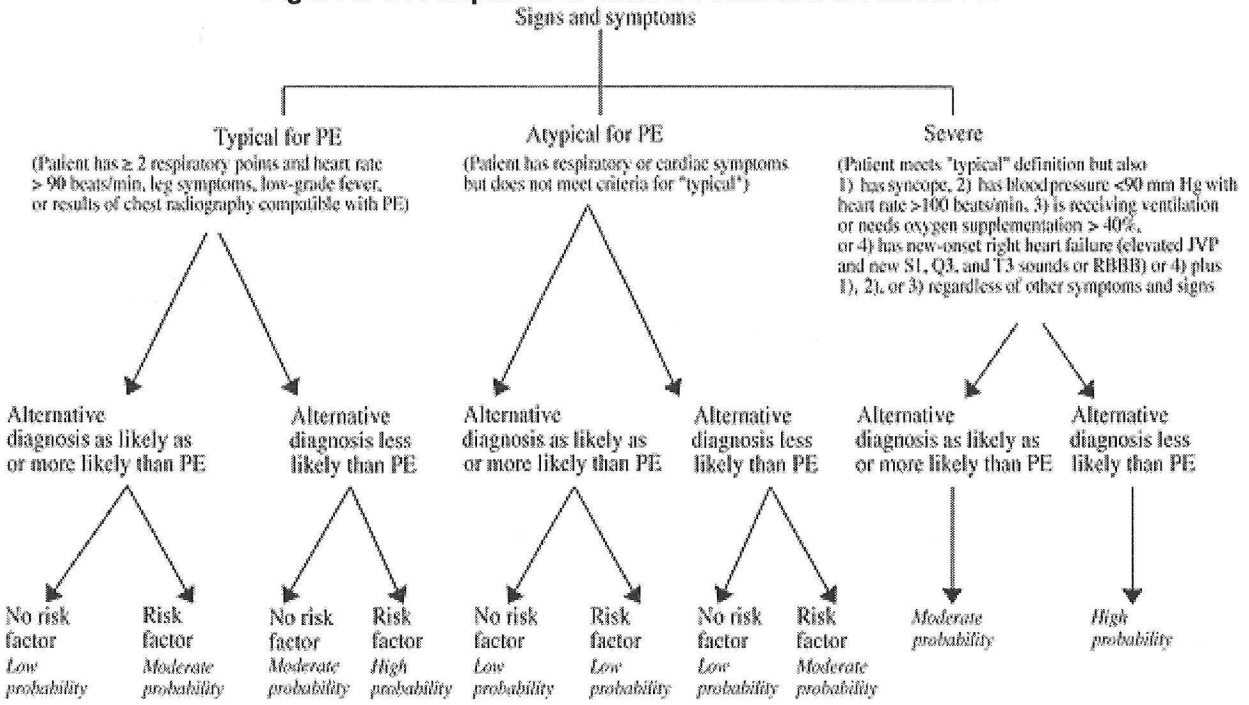
Several other noninvasive tests are available to help avoid the uncertainties. These tests can either supplement or substitute for scintigraphy in different populations. In evaluating the utility of a diagnostic

test we have to not only consider the sensitivity and specificity of a test, which define the inherent quality of a test and its performance in health or disease, but also the predictive value of a positive or negative test. The predicitive value of a test is affected by the prevalence of the disease in the group that is being tested or the probability of the disease in a given patient. The positive predictive value (PPV) of a test with high specificity will decrease when the disease prevalence is low and the NPV of a very sensitive test will decrease when the disease prevalence is high. PIOPED study highlighted the importance of pretest probabilities in making clinical decisions based on scan results.

The clinical probability of PE can be based on a set of information – history, physical examination, arterial blood gas, chest radiographs and electrocardiograms, but without a standardized diagnostic algorithm a clinician's estimation may be unreliable and difficult to reproduce. How do we assess the clinical probability of PE in a given patient? What are the clues one looks for in considering PE as a possible diagnosis? How accurate and reliable are they? How important is the clinical assessment of the pretest probability of PE in the final outcome? In other words, how accurate is the clinician's initial diagnostic impression of the presence of absence of PE in a patient? In an attempt to standardize the process of assigning pretest probabilities to patients who present with signs and symptoms that are suspicious for PE various clinical prediction models have been developed (25, 26).

Clinical prediction Model for PE

Figure 3. Development of Clinical Prediction Model for PE



Respiratory points include the following:
Dyspnea or worsening of chronic dyspnea
Pleuritic chest pain or nonretrosternal and nonpleuritic chest pain
O2 saturation <92% on room air that corrects with less than supplemental oxygen
Hemoptysis
Pleural rub

Risk factors include the following:
Surgery within 12 weeks
Immobilization for 3 or more days in the 4 weeks before presentation
Previous VTE
Family history of thrombophilia
Cancer (active, treated within months or in palliative stages)
Postpartum period
Lower extremity paralysis

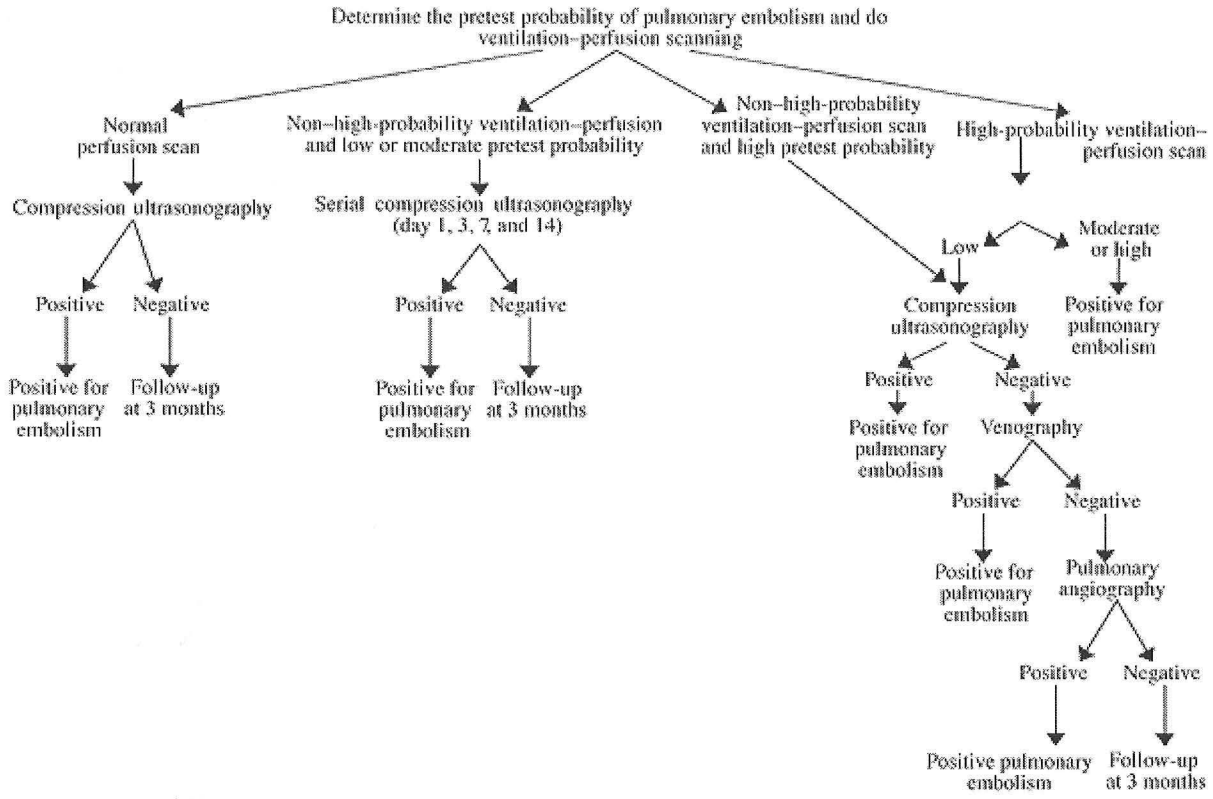
Wells and colleagues from Canada developed and validated a clinical prediction model for the diagnosis of PE that clearly stratifies patients into 3 distinct groups (Figure 3) (25). A scoring system was developed based on well established risk factors for PE, clinical signs and symptoms, and the determination of whether an alternative diagnosis was likely, to categorize a patient as having low, intermediate or high pretest probability of PE. The model was tested in a pilot study on 91 patients and then validated prospectively in 1239 consecutive outpatients and inpatients with suspected PE in 5 hospitals. All patients underwent V/Q scan and bilateral CUS. V/Q scans were interpreted as normal, non-high probability for PE or high probability for PE according to Hull criteria. PE was diagnosed or ruled out by V/Q scan, and depending on the lung scan results, a combination of serial lower extremity venous ultrasonography, ascending venography and pulmonary angiography as well as 3 month follow-up for clinical evidence of VTE (Figure 4). Pulmonary embolism was diagnosed in 3.4% of the 734 patients with a low pretest probability, 27.8% of 403 patients with moderate pretest probability and 78.4% of 102 patients with a high pretest probability (Table 6). The difference in prevalence of PE in the three categories was statistically significant ($p < 0.001$). The proportion of patients with PE in the 3 categories was similar in all five centers and the weighted *k* value for interobserver agreement for the clinical model was 0.86 attesting to the reproducibility and reliability of the model.

This model was further simplified and an easy to use scoring system was developed (27). Using stepwise logistic regression on variables that were significantly associated with PE in the original model statistically significant variables were identified and assigned points based on the regression coefficient. (The investigators performed a univariate regression analysis to identity the variables that were significantly associated with PE in the original model to include in a stepwise logistic regression. Seven variables with p values <0.05 were identified and were assigned points for the clinical prediction model by doubling the regression cooefficient value for each variable and rounding to the nearest 0.5) (Figure 4). Cut points were created to classify patients as having low, moderate and high probability of PE with rates similar to those obtained in the original study i.e. 3%, 28% and 78% respectively. The model was derived on a randomly selected 80% in the original study population (the derivation set) and applied to the remaining 20% of study patients (validation set). Patients with a score of <2 points had a low probability of PE with diagnosis of PE confirmed in 3.6% in the derivation set and 2% in the validation set. Patients with a score of 2 to 6 had a moderate probability of PE with diagnosis of PE confirmed in 20.5% in the derivation set and 18.8% in the validation set. Patients with a score of >6 had a high probability of PE with the diagnosis confirmed in 66.7% in the derivation set and 50% in the validation set. The model has since been validated in another 946 consecutive, symptomatic patients presenting to the emergency department. (28).

Figure 4. Simplified Clinical Prediction Model for PE (27)

Variable	**Points**
• Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of deep veins)	3.0
• An alternative diagnosis is less likely than PE	3.0
• Heart rate greater than 100	1.5
• Immobilization or surgery in the previous 4 weeks	1.5
• Previous DVT/PE	1.5
• Hemoptysis	1.0
• Malignancy (on treatment, treated in the last 6 months or palliative)	1.0
Score	**PE Rate (95% CI)***
<2 (Low)	3.6% (2.0,5.9)
2-6 (Moderate)	20.5% (17,24)
>6 (High)	66.7% (54.3,77.6)
P<0.001 for the 3 groups	

Figure 5. Using Clinical Probability Model for Managing Patients with Suspected PE *



*In clinical practice patients with normal perfusion scan do not need any further testing.

In the study by Wells et al 665 patients with non-high probability scan, low or moderate pretest probability by the clinical prediction model, and negative serial CUS were followed for 3 months without anticoagulant treatment (Figure 5). Three of the 665 (0.5%, 95% CI 0.1% to 1.3%) developed recurrent VTE compared to 2 of 332 patients (0.6%, 95% CI 0.3% to 3%) with normal scan and normal initial CUS (25). Thus treatment can safely be withheld in patients with non-high probability lung scan and low or moderate pretest probability if CUS is negative. Only patients with discordance in pretest probability and V/Q scan results (low clinical probability and high probability scan or high pretest probability and a non-high probability scan) will require further testing with venography and/or pulmonary angiography if CUS is negative. They were able to reliably diagnose or exclude PE in 96% of patients by using pretest probability estimate, V/Q scan and bilateral leg CUS. Only 46 of 1239 patients (3.7%) required venography or angiography. Thus combining clinical probability estimates and a non-invasive strategy of ventilation perfusion scan and serial leg CUS pulmonary embolism can be reliably diagnosed or excluded in a majority of patients (29).

While limiting serial testing to one repeat study between 7-10 days appears safe in patients with symptomatic DVT, the noninvasive strategy for patients with PE was done with serial testing for 14 days (days 3, 7 and 14) with 25% of serial conversion occurring on day 7 and another 25% on day 14. This is still inconvenient and expensive and may miss the small minority of patients with thrombosis limited to pelvic veins and also emboli arising from DVT in the upper extremities, the relative incidence of which is rising (30, 31). Can serial testing be avoided and can thrombi in sites other that lower extremities be diagnosed noninvasively?

D-dimer Assay

D-dimers are specific degradation products of crosslinked fibrin and one of the last products derived from activation of coagulation and subsequent fibrinolytic process. They consist of 2 identical subunits

derived from 2 fibrin molecules and are sensitive markers of thrombosis. Measurement of D-dimers has been facilitated by the development of monoclonal antibodies that bind to epitopes on D-dimer fragments that are absent of fibrin, fibrinogen and non cross-linked fibrin. Patients with VTE have approximately 8 fold elevation of D-dimers with levels remaining persistently elevated in 80% at one week and in 39% at one month (32). Heparin therapy can cause a slight fall in level within 24 hours but remains above normal. In patients with proven pulmonary embolism D-dimer level of > 500ng/mL measured by enzyme linked immunosorbent assay (ELISA) had a sensitivity of 98% and specificity of 39% with a PPV and NPV of 44% and 98% respectively (33,34). Conditions other than VTE can cause elevated D-dimer levels (Table 6). Many of these conditions are also associated with increased risk of VTE and thus D-dimer measurement has low specificity for PE and cannot be used to rule in a diagnosis of PE. The high sensitivity and negative predictive value of D-dimer test makes this a useful tool for rapidly ruling out the diagnosis of PE.

Table 6. Conditions associated with increased D-dimer levels
Recent surgery or trauma (within 10 days)
Recent myocardial infarction (within 10 days)
Acute infection
Disseminated intravascular coagulation
Pregnancy or recent delivery
Active collagen vascular disease
Metastatic cancer

While conventional ELISA assays can detect D-dimer in concentrations as low as 30-80ng/ml, clinical studies of PE have reported the highest sensitivity ranging from 95-98% and NPV of 91-97% at a cut off value of 250-500 ng/ml and are considered the gold standard. However, ELISA tests are labor intensive, have slow turn around time and are suitable for batch analysis and thus are not very useful for rapid clinical decision making. Latex agglutination tests are rapid, quantitative or semi-quantitative based on serial dilution but have a lower sensitivity. The different types of commercially available assays use different methodological techniques and have different test characteristics; assays are not standardized, cut off values range from 250-500 ng/mL (some results are expressed as ng/mL FEU or fibrinogen equivalent units, 1 ng/mL FEU being = to 2 ng/mL D-dimer unit). Correlation between the different latex agglutination assays is poor and results from one assay cannot be extrapolated to another assay. Sensitivity, specificity, PPV and NPV for PE for the different latex agglutination assays range from 88-96%, 47-61%, 56-67% and 83-94% respectively(35).

Prospective studies have shown the safety of withholding anticoagulant treatment based on a negative D-dimer test using the sensitive ELISA D-dimer assay (Asserachrom D-Di, Diagnostica Stago, France). Of 671 outpatients presenting to the emergency room with clinical suspicion of PE in one study the diagnosis was ruled out and anticoagulant treatment was withheld in 198 patients (29%) who had D-dimer level <500ng/mL. One patient developed VTE during the 3-month follow-up, for a NPV of 99.5% (95% CI 97-100%). The prevalence of PE in the entire group was 29% (36).

Several new tests, including a rapid ELISA test, a new bedside assay using capillary whole blood and second generation semi-quantitative latex agglutination tests based on immunofiltration or immunoturbidimetric analysis have become available (Table 7).

Vidas ELISA D-dimer assay (Vidas DD, bioMerieux SA, France), a new, automated rapid ELISA test with results that can be made available within 2 hours, has demonstrated sensitivity of 100% in patients with documented venous thromboembolism (VTE) (35, 37). SimpliRED D-dimer test (SimpliRED whole blood agglutination D-dimer test, AGEN Biomedical, Ltd, Brisbane, Australia) is a latex agglutination test that uses a bispecific reagent with a monoclonal antibody to human red blood cells and a monoclonal antibody to D-dimer. Addition of the reagent to a drop of whole blood results in visible red blood cell agglutination in the presence of elevated D-dimer levels in the sample. The test can be performed at the bed side on whole blood obtained from finger stick or venipuncture and can be read within 2 minutes as positive or negative and has a sensitivity of 85-90% and specificity of 68% for PE (29, 38).

Clinical management studies using the Vidas ELISA and SimpliRED D-dimer assay have been performed. Perrier et al prospectively evaluated 918 patients with clinically suspected DVT or PE (444 patients with PE) presenting to the emergency department using a sequential noninvasive strategy. Patients with D-dimer level <500ng/mL by Vidas ELISA were considered not to have VTE and were followed without anticoagulant treatment for 3 months. Patients with D-dimer >500ng/mL had CUS, clinical probability assessment and V/Q scan in a diagnostic algorithm. The NPV for VTE on follow-up in 286 patients with a d-dimer level <500ng/mL was 99.3%, of which 159 patients were in the PE group (39). Diagnosis was made non-invasively in 94% of the entire cohort with only 5% requiring pulmonary angiography.

The SimpliRED D-dimer assay was used in combination with clinical probability estimates to rule out the diagnosis in patients presenting to the emergency department with suspected PE. Of 930 consecutive patients in one study PE was ruled out on the basis of low clinical probability and negative D-dimer assay in 437 patients (46%). One patient developed PE during follow-up giving a NPV of 99.5% (95% CI 99.1 to 100%). The NPV of the d-dimer test was 97.3% (95% CI 95.8% to 98.4%) in the entire cohort, 93.9% (CI 89.8 to 96.7) in the moderate-probability group, and 88.5% (CI 69.9% to 97.6%) in the high-probability group (28). NPV pf SimpliRED D-dimer assay was only 83% in another study of 125 patients presenting to the emergency department with suspected PE where patients were evaluated with a combination of V/Q scan, CUS or pulmonary angiogram without estimating prestest probability (40). The prevalence of PE in the entire cohort was 30%, a rate similar to the high pretest probability group in Wells' study that showed a NPV of 88% for the D-dimer in this cohort (28).

The second generation quantitative latex agglutination tests based on immunoturbidimetric technique have shown high sensitivity and NPV (excess of 95%) in patients with confirmed PE where the diagnosis was made on the basis of a combination of lung scan, CUS and pulmonary angiogram. The cut off value for these tests in different studies has varied from 180 to 500ng/mL of D-dimer to 500FEU ng/mL (41, 42). The tests are fully automated and thus more reliable. Tinaquant latex D-dimer test and MDA D-dimer test at a cut off of 500 FEU ng/mL were used for clinical decision making to withhold anticoagulant treatment in patients with a non-high probability of DVT and a negative D-dimer test in two studies recently. The TinaQuant assy had a NPV of 99.4% (95% CI 96.9-100%) (1 of 176 patients developed symptomatic thrombosis during follow-up) and the MDA D-dimer assay had a NPV of 99.6% (CI 98.1-100) (1 of 283 patients developed symptomatic DVT during follow-up). Thus the new second-generation latex agglutination assays appear promising in ruling out DVT in patients with low pretest probability (43, 44). Similar studies in patients with suspected PE have not been published.

Thus it appears that D-dimer tests such as classic ELISA assays and the Vidas rapid ELISA test can be used safely as stand alone tests to rule out PE in outpatients. The rapid, bedside agglutination test (SimpliRED assay) can be used to rule out PE in patients with a low pretest probability. The sensitivity and NPV of this assay is not high enough to rely on this test in patients with moderate or high clinical probability of PE. Simpli-RED D-dimer test may nevertheless simplify the testing strategy for DVT in patients presenting with symptoms of PE by eliminating the need for serial CUS if initial ultrasound and D-dimer test are both negative. This strategy was proven to be safe in the management of patients with suspected DVT (45). Clinical management studies have shown that further diagnostic tests may be spared in 30-35% of patients presenting to the emergency department with clinical suspicion of PE (39, 46). Given the low specificity, D-dimer assays are not as useful in in-patients who are more likely to have other co-morbidities leading to false positive test. Fewer patients will be spared further diagnostic tests for PE in this setting. The role of new, second generation latex agglutination tests remains to be evaluated in clinical management studies (Table 8).

Thus outcome studies using a combined non-invasive strategy that includes clinical probability assessment, V/Q scan, CUS and D-dimer assay have shown that an accurate diagnosis can be made in the majority of patients. It is safe to withhold treatment in patients who are ruled out for PE using this strategy. Pulmonary angiogram will be required in a minority (4-11 %) of patients (27, 28, 39).

Table 8. Characteristics of the Different D-dimer Tests				
Technique	**Example**	**Sensitivity**	**Specificity**	**Comments**
Microplate ELISA	Asserachrom Fibrinostika-FbDP	High	Low	Gold standard Not widely available Cumbersome, suitable for batch analysis Negative test can rule out VTE
First generation Latex agglutination assays	Dimertest latex D-dimertest	Intermediate	Intermediate	Rapid Sensitivity and NPV too low for clinical use in VTE
Rapid ELISA	Vidas ELISA	High	Low	Rapid, automated, single sample assay Tested in clinical management studies Negative test can r/o VTE in patients with low clinical probability
Whole-blood agglutination	Simpli-RED	Intermediate To High	Intermediate	Rapid, bedside Tested in clinical management studies Negative test can r/o VTE in patients with low clinical probability
Second generation latex agglutination	TinaQuant Liatest MDA D-dimer	High	Intermediate	Rapid, semi-quantitative No clinical management studies for PE
Membrane ELISA	NycoCard	High	Low	Rapid, suitable for real-time use

Spiral CT Angiography

The introduction of helical or spiral CT scanning techniques in 1990 revolutionized the ability to image the pulmonary arteries non-invasively during a single breath hold and optimal contrast enhancement. SCTA is replacing V/Q scan as the test of first choice in the non-invasive evaluation of patients with suspected PE.

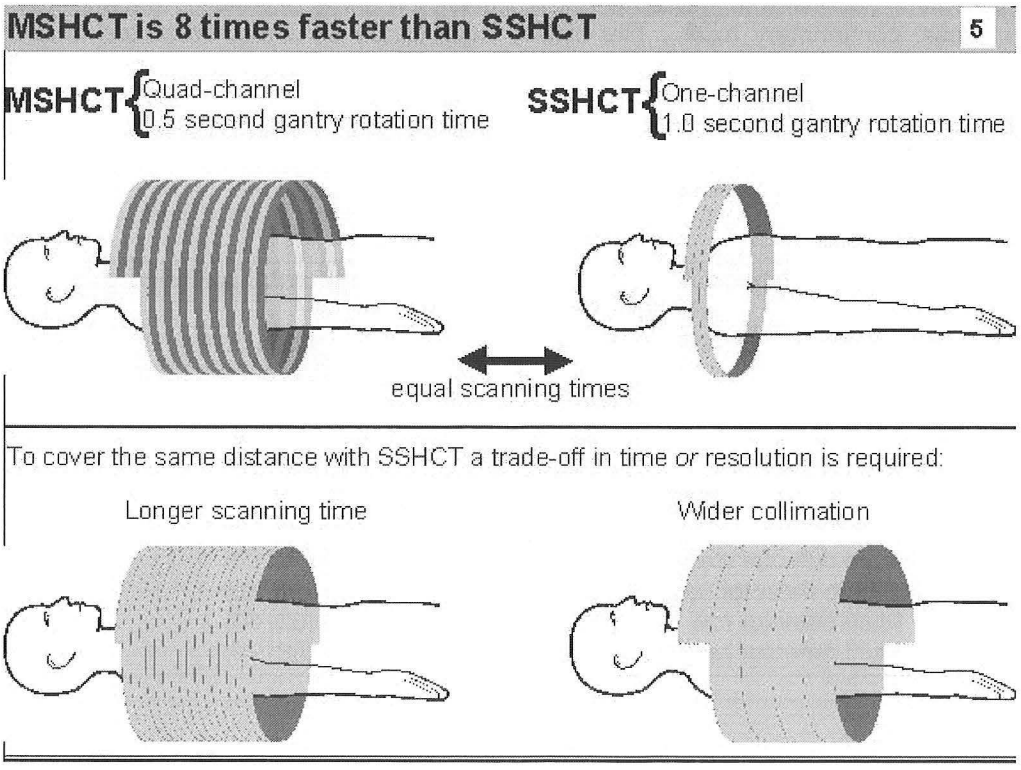
Remy-Jardin first investigated the role of SCTA in evaluating patients with suspected PE and showed sensitivity of 100% and specificity of 95% for detecting emboli in the central (main, left, right, and lobar) pulmonary arteries compared to pulmonary angiogram (47). He also described in detail the spiral CT protocol for imaging that consists of three parts; data acquisition, data processing and data display. Data is acquired volumetrically by a fast spinning x-ray source and detector by scanning a distance of 10-12 cm from the aortic arch to 2 cm below the level of the inferior pulmonary veins in a single breath-hold lasting 15-20 seconds. Vessel opacification is achieved by the injection of 120-150 mL of 30% nonionic contrast agent at 2-5mL/sec and a scanning delay of 12-15 seconds. Most radiologists prefer scanning in the caudocranial direction in order to avoid motion artifacts affecting the lower lobe arteries towards the end of breath-hold. Rate of table feed (mm/second) through the gantry, rotation speed and collimation (beam thickness) determine the quantity of data acquired and thus the image quality. Scanning delay after beginning contrast injection has to be adjusted to the patient's condition, with shorter scanning delay for younger patients with hyperdynamic circulation and greater scanning delay for older patients and those with congestive heart failure. Transverse CT data sets that are acquired digitally can then be processed and reformatted to obtain saggital, coronal or 3 dimensional images and displayed and viewed in real time at a workstation. Scanning for PE requires meticulous attention to technique with adequate enhancement of pulmonary arteries, thin collimation and high pitch, with pitch defined as table travel in mm per gantry rotation divided by beam collimation in mm. CT criteria for acute PE include central or eccentric partial intraluminal filling defects surrounded by contrast-enhanced blood, complete vessel occlusion by low-attenuation material or "rail-road track" sign formed by long mural thrombi with surrounding contrast enhanced blood (48). Ancillary signs of wedge-shaped pleural-based consolidation, pleural effusion, and dilated central or segmental pulmonary arteries may be detected on spiral CT further supporting the diagnosis of PE when visualization of vessels is sub-optimal. Small hilar lymph nodes

and partial volume averaging of horizontally or obliquely oriented arteries may give rise to pseudo filling defects resulting in false positive signs of PE.

Table 9. Role of SCTA in the diagnosis of PE: Systematic Review*			
	Sensitivity	**Specificity**	**Reference Standard**
Rathbun et al (49) 15 studies from 1992-1999	53-100	81-100	Pulmonary angiography or Combination of tests
Mullins et al (50) 11 studies from 1992-1998	64-93%¶	89-100%	Pulmonary angiography
*None of the studies met all standard criteria for diagnostic tests ¶ Sensitivity was 29% for subsegmental arteries			

SCTA did not fare as well in subsequent studies as shown by two simultaneous reviews in 2000 (49, 50) (Table 9). The authors reviewed studies published between 1992 and 1999 that met established methodological standards for evaluation of diagnostic studies and identified 11 and 15 studies each that met some, but not all of the criteria. Reported sensitivity and specificity of SCTA for PE ranged from 53 to 100% and specificity from 81 to 100%. This raises questions about the reliability of spiral CT as the sole diagnostic test for PE. While differences in spiral CT protocols, reference standard used (pulmonary angiography, high-probability V/Q scan or a diagnostic algorithm that included V/Q scan, CUS and pulmonary angiogram), and the spectrum of disease in the study populations most likely contributed to the reported differences in study outcomes, the wide variability in the results is also attributed to limitations of earlier CT scanners in detecting segmental and subsegmental pulmonary arteries. In fact, when evaluation was limited to the central pulmonary arteries (from the main to the 4th order segmental arteries) sensitivity and specificity was higher, ranging from 83-100% and 92-100% respectively. Technology has evolved considerably since these studies, which used single slice detectors with about twenty 6-mm sections to cover the 12 cm length of lungs.

Figure 6. Advantage of Multislice helical CT scanner



More recent studies have used dual section helical CT scanners with double-array detector system to obtain ~80 overlapping 3-mm CT sections to cover 16cm of the lung, providing wider coverage and reducing the effective section thickness and greater ability to image 5th order subsegmental arteries. Table 10 lists sensitivity, specificity and NPV of SCTA in the diagnosis of PE from more recent studies performed with 2-3 mm collimation (46, 51-53). Three of the four studies showed sensitivity of 90-94% and NPV of 94-96%. NPV for CT was based on 3-month follow-up data in three of the four studies (46, 51, 53). The study by Perrier et al showing a much lower sensitivity and NPV had several methodological problems. Although this was a prospective study, only about 25% of patients were included in the final analysis. A sensitive ELISA D-dimer assay was used to rule out PE In 35% of the initial 1100 patients. CT angiogram could not be performed in more than 50% of the remaining patients, raising questions about the validity of the results. In the study by Qanadi et al, sensitivity and specificity increased from 90 and 94% to 97 and 98% respectively when subsegmental PE was excluded.

Table 10. Thin slice Helical CT in the diagnosis of pulmonary embolism

Study	Number	Consecutive	Reference test	Sen	Spec	NPV
Blachere et al (51)	179	Yes	Combination of tests	94	93	96
Qanadi et al (52)	158	Yes	Pulmonary angiogram	90	94	94
Perrier et al (46)	299	No¶	Combination of tests	70	91	81
Nilson et al (53)	90	Yes	Pulmonary angiogram	91	96	95
¶ Prescreened with negative D-dimer. Number represents <50% of total D-dimer negative patients						

Subsegmental PE

How important is it to detect subsegmental emboli and what is their clinical significance?

Reported prevalence of subsegmental PE ranges from 6% to 40%. PIOPED study showed that PE limited to subsegmental arteries was most prevalent among patients with low-probability V/Q scan, particularly if they had no prior cardiopulmonary disease. Other studies have shown the prevalence to be as high as 30% in patients with indeterminate V/Q scan, the group of patients that are most in need of other non-invasive confirmatory tests. The clinical significance of emboli restricted to subsegmental pulmonary arteries is also controversial. While small subsegmental emboli may be very common and of no consequence in most healthy people the burden of even small emboli, however, may be severe in patients with underlying cardiopulmonary disease, especially if they are multiple, or are likely to recur. The short and long-term complications of undiagnosed and untreated episodes of subsegmental PE may be severe or even fatal in such patients (9, 54, 55).

Table 11. Proportion of well-visualized subsegmental pulmonary arteries with three CT techniques

Reader and CT technique	Collimation (mm)	visualized arteries % (95% CI)
1 single detector row	3	37 (34, 41)
Multi-detector row	2.5	56 (52, 59)
Multi-detector row	1.25	76 (73, 79)
2 Single-detector row	3	39 (35, 42)
Multi-detector row	2.5	53 (49, 56)
Multi-detector row	1.25	78 (75, 80)
3 Single-detector row	3	39 (35, 42)
Multi-detector row	2.5	56 (53, 60)
Multi-detector row	1.25	71 (68, 75)
Ref 56		

Multislice, multidetector CT scanners with 4 detectors providing 1-1.25mm collimation are already being used with substantially higher detection rates for subsegmental pulmonary emboli and greater interobserver agreement (Table 11) (56, 57). These new scanners can capture 4 simultaneous slices in 0.5 seconds compared to 1 slice per second by the old scanners, allowing greater data acquisition at a faster rate. Eight, 16 and 32 slice detectors will soon be available with the ability to detect even the tiniest of clots.

Outcome in patients with negative SCTA appears to be similar to those with normal V/Q scan with less than 2% risk of VTE on follow-up in more recent studies (Table 12) (58-59).

Table 12. Outcome in patients with negative Helical CT or V/Q scan

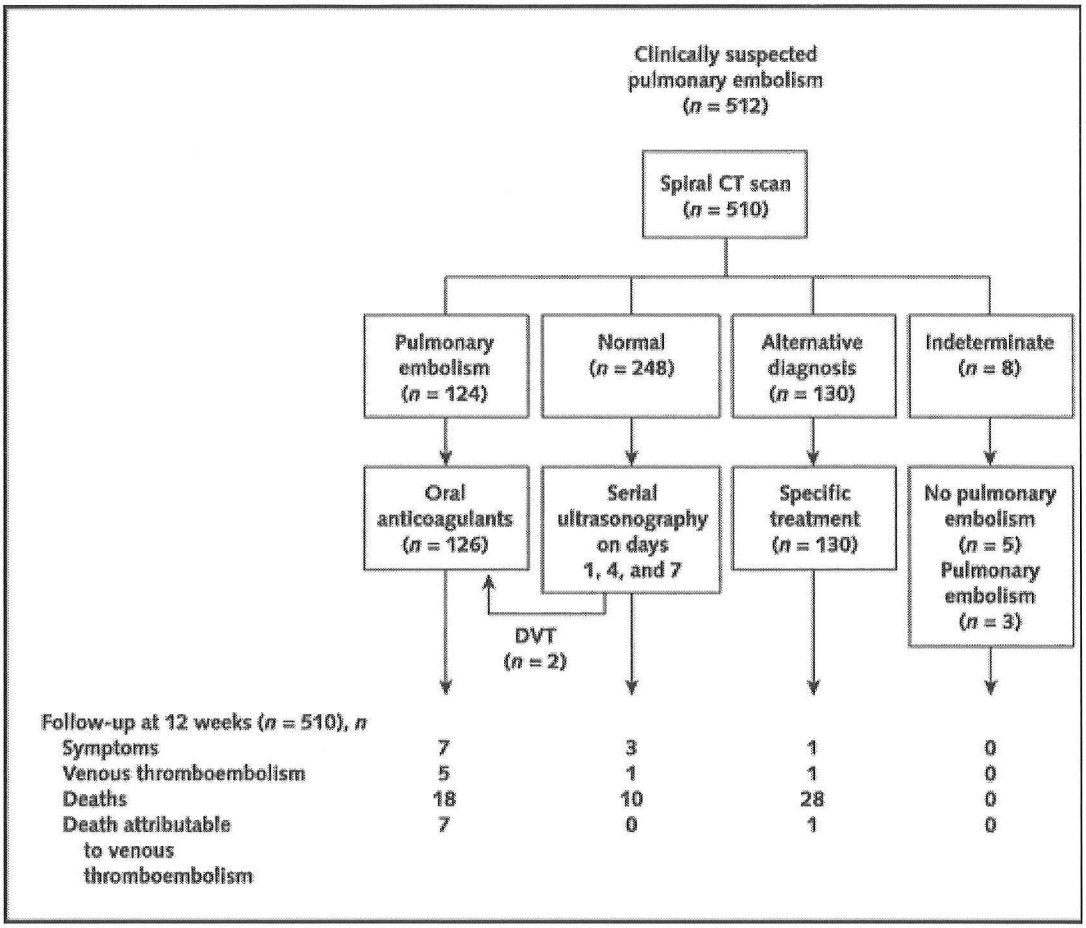
	Neg CT	Low Prob V/Q scan	Normal V/Q scan
Completed 3m f/u	198	162	188
Rec PE	2 (1%)	0	5 (3.1%)
NPV	99%	100%	97%
41% in CT group and 22% in Low Prob V/Q scan group also had CUS			
Ref 59			

The ANTELOPE (Advances in New Technologies Evaluating the Localisation of Pulmonary Embolism) trial was a prospective management study evaluating the utility of spiral CT scan as the initial test in patients with suspected PE (Figure 7) (60). This multi-center study from the Netherlands enrolled 510 consecutive inpatients and outpatients with suspected PE. All underwent helical CT of the pulmonary arteries within 24 hours of presentation using a single-detector scanner with 5mm collimation and 3mm image reconstruction. Patients were stratified into PE+, PE-, and alternate diagnosis group on the basis of the results of the initial CT. PE+ patients were treated with anticoagulants, PE- patients underwent serial CUS on days 1, 4 and 7. All patients were followed for 3 months for signs and symptoms of VTE (completed in100% of patients). CUS or venography was performed for suspected DVT and pulmonary angiography for suspected PE during follow-up. PE was diagnosed on the basis of initial CT in 124 of 510 patients for a prevalence of 24.3% in the entire group, a figure that is comparable to the PIOPED study. An alternate diagnosis was revealed in 26% patients with negative PE. Thus helical CT was diagnostic in about 50% of patients suspected of PE. DVT was diagnosed by CUS on day 1 in 2 of 248 patients who were PE- and were treated with anticoagulants. The incidence of clinical VTE with three-month follow-up in the remaining 246 (48.8% of the entire cohort) patients who were not treated with anticoagulants was 0.4% (95% CI, 0% to 2.2%). In the group of 376 patients who were not diagnosed with PE and thus not treated with anticoagulants (PE- and alternate diagnosis group) the incidence of clinical VTE during the 3-month follow-up was 0.8% (CI, 0.2% to 2.3%). Thus spiral CT with single detector scanner appeared to be safe as an initial diagnostic test in patients with suspected PE with a NPV of 99.5%. The 2 episodes of DVT in the PE- group were diagnosed by the initial CUS. No DVT was diagnosed on serial ultrasound. Assuming that CUS was not performed and the 2 patients with DVT were misdiagnosed initially and detected at follow-up, the rate of VTE for the entire group of 376 patients not treated with anticoagulants on the basis of the SCTA alone was 1.3% (5 of 376 patients; CI 0.4% to 3.1%), (NPV 98.6%).

SCTA with the new generation scanners appears to be superior to V/Q scan as an initial test and often the only test in the diagnostic evaluation of PE with more patients being accurately diagnosed as PE+ or PE- with SCTA than with V/Q scan alone (51, 61). An alternate diagnosis is revealed in 25-65% of patients who are negative for PE on SCTA (60-62). However 12-24% of patients with suspected PE may have contraindications to SCTA (abnormal renal function, contrast allergy, pregnancy etc) and will require other diagnostic tests. SCTA may be technically inadequate for accurate interpretation in another 4-5% of patients, a rate similar to the 3% reported for pulmonary angiogram (9, 46, 63).

Performing CT venography by scanning the lower extremities from the knee to lower abdomen 3 minutes after the same contrast injection used for chest scanning to evaluate the deep venous system has been explored in some small studies with promising results (64).

Figure 7: Helical CT as the primary diagnostic test in suspected PE. The ANTELOPE Study



Questions about the role and place of spiral CT angiography in the diagnostic management of PE remain. PIOPED II is a multicenter prospective investigation sponsored by the National Heart, Lung, and Blood Institute that hopes to clarify the role of SCTA in venous thromboembolism. This ongoing study will enroll 1,068 patients over 18 months and will evaluate whether (1) spiral CT can be used as a definitive diagnostic test to replace V/Q lung scans and pulmonary angiograms in patients with suspected PE; (2) spiral CT may be used as a definitive test in patients with nondiagnostic V/Q scans; (3) spiral CT may be used as a definitive test to diagnose (but not exclude) PE; (4) spiral CT may be used to exclude (but not diagnose) PE; and (5) spiral CT may be used as a definitive diagnostic test to diagnose PE in central pulmonary arteries, requiring additional tests to exclude PE in segmental or subsegmental arteries. Multislice scanners with 1-1.25 mm collimation will be compared with a composite reference test for venous thromboembolic disease based on V/Q scan, venous CUS, digital subtraction angiography, and contrast venography (65).

Magnetic Resonance Angiography (MRA)

MR imaging is evolving as another valuable non-invasive means of detecting PE. Advances in magnetic resonance hardware and use of gadolinium enhancement have made possible high-resolution pulmonary

angiography during single breath holding. Small studies comparing MRA with pulmonary angiogaphy have shown sensitivity of 85-100% and specificity of 62-90% (66-69). In a study of 30 patients referred for pulmonary angiography for suspected PE, MRA identified all 5 lobar and 16 or 17 segmental emboli detected by conventional angiogram in 8 of 30 patients. Sensitivity for PE among 3 reviewers was 100, 87, and 75% and specificity 95, 100 and 95% respectively. The inter-observer correlation showed a k of 0.49 to 1.0 for main and lobar vessels and 0.40 to 0.81 for segmental vessels. Subsegmental vessels were not reported (70). MR venography has been proven to be as accurate as Doppler US in detecting DVT (71). New "blood pool" contrast agents like NC100150 (CLARISCAN™, Nycomed Amersham, Oslo, Norway) that have a long intravascular half-life of 2.7-4 hours allow for accurate delineation of both arteries and veins. With the ability to image pulmonary arteries and the veins of the lower extremities MR imaging with such agents has the potential to be used as a "one-stop shopping" tool for the evaluation of patients with suspected VTE (72). The role of MRA in the evaluation of patients with PE remains to be validated in well-designed clinical studies.

Electron Beam CT scan (EBCT)

This is the latest in CT technology with scanning times of 50-100ms. Although these scanners are not widely available preliminary studies comparing EBCT with conventional angiogram and SCTA have shown favorable results in visualizing pulmonary vasculature (73, 74). The safety of withholding anticoagulant therapy after a negative electron beam CT angiography was shown in a retrospective analysis of 1010 from the Mayo clinic. Three month cumulative incidence of VTE in this group of 1010 patients was 0.5% (95% CI 0.0% to 0.7%) (75).

Echocardiography

No prospective studies have evaluated the role of echocardiography in the diagnostic management of patients with suspected PE. Right ventricular (RV) failure is the cause of death in patients with fatal PE. Evidence of elevated pressure in the right side of the heart or acute right ventricular dysfunction (right ventricular dilatation and hypokinesis, septal flattening and paradoxical septal motion, diastolic left ventricular impairment, pulmonary arterial hypertension detection by Doppler flow velocity and patent foramen ovale) can be detected by transthoracic echocardiography (TTE) in patients with massive pulmonary emboli (occlusion of >30% of vascular bed) and in patients with recurrent PE and can provide prognostic information that may influence management (76, 77). In a prospective study of 209 consecutive patients with documented PE, even normotensive patients with echocardiographic evidence of RV dysfunction had higher in-hospital mortality (78). Compared to SCTA, sensitivity and specificity of esophageal echocardiography (TEE) was 80% and 100% respectively in a subset of patients with suspected massive PE (79). Bedside evaluation with echocardiography (TTE or TEE) may also enable direct visualization of free-floating thrombus in the right heart in severely ill patients who are too unstable to undergo other imaging studies (80).

Table 12. Criteria for Diagnosis or Exclusion of PE

Definite PE +	Definite PE -
Positive Pulmonary Angiogram High Probability V/Q Scan with moderate or high clinical probability Non-diagnostic V/Q scan with positive CUS Positive SCTA	Normal Pulmonary Angiogram Normal V/Q Scan Low Probability V/Q scan with low clinical probability Normal ELISA D-dimer assay Non-diagnostic V/Q scan and negative CUS with low or moderate clinical probability Negative SCTA (multidetector scans)

Figure 8a. Diagnostic Approach to Patients with Suspected PE

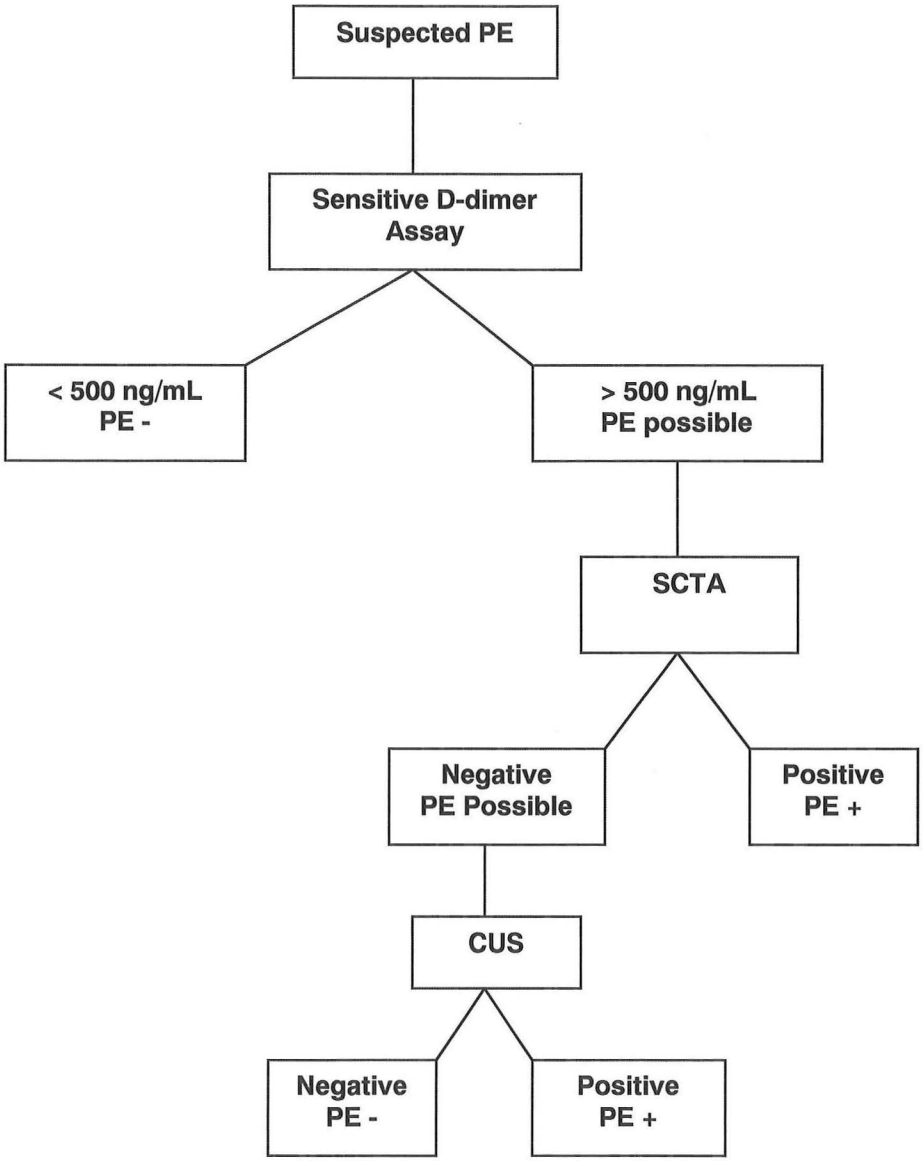
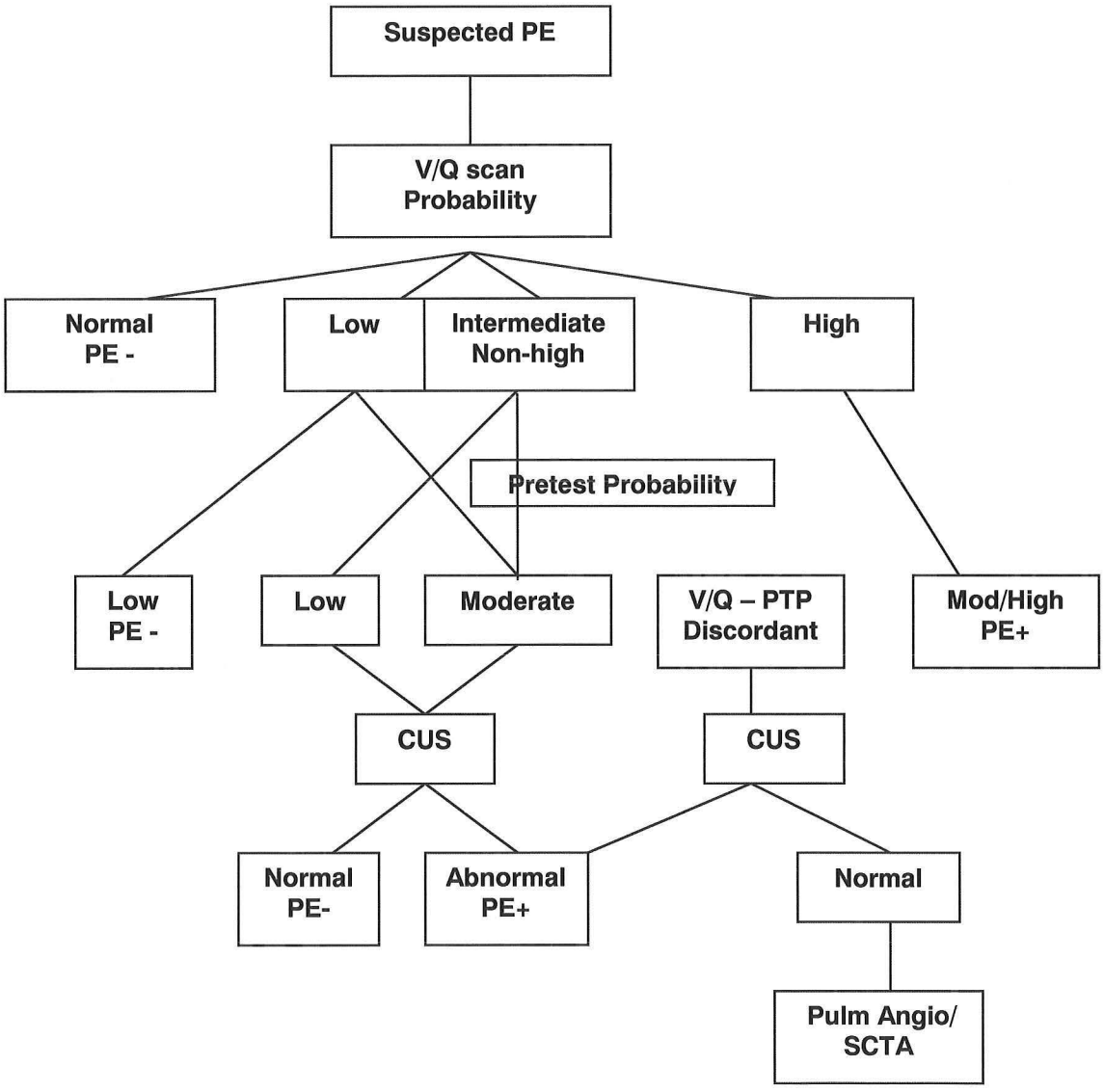


Figure 8b. Diagnostic Approach in Patients with Suspected PE



Cost effectiveness analysis based on decision models has also shown that using SCTA in conjunction with sensitive D-dimer assays or in patients with non-diagnostic V/Q scan is more cost effective. Based on lower sensitivities from earlier studies, spiral CT as a single test was not cost effective, but this may change in the future (81, 82).

PE can be reliably ruled in or ruled out when any of the following conditions are met (Table 12).

In summary, an accurate diagnosis can be made in over 95% of patients with suspected PE utilizing clinical probability estimates and a combination of non-invasive tests that include D-dimer assay, V/Q scan, CUS of the lower extremities and SCTA. The choice of test and the order of testing will depend on resource availability and patient characterisitcs (Figure 8a-b). With appropriate use of these tests, pulmonary angiogram will be required in less than 5% of patients (63).

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