

New Diagnostic and Treatment Modalities for Pulmonary Embolism: One Path through the Confusion

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Abstract

Pulmonary embolism is one of the greatest diagnostic challenges in emergency medicine. New techniques and strategies constantly arise for the diagnosis and treatment of this disease. A review of the new diagnostic and treatment modalities for pulmonary embolism (PE) suggests that it should be suspected in any patient with unexplained dyspnea, tachypnea, or chest pain. All patients suspected of PE must be risk stratified, ideally with a criteria-validated clinical decision rule. After assessing pre-test probability, D-dimer assays will reliably exclude PE in the low risk group and no further imaging is warranted. Computed tomography (CT) angiogram is the initial imaging study of choice for stable patients. V/Q scans should be used only when CT is not available or if the patient has a contraindication to CT scans or intravenous contrast. Bedside echocardiography or stabilization of the patient and CT angiogram are the initial tests for suspected massive PE. If PE is confirmed, hypotensive patients should be treated with thrombolytics. Both heparin and low molecular weight heparin are equally effective initial treatments for stable patients with suspected or confirmed PE.

Because accurate screening and identification of pulmonary embolism frequently requires more than a single test, knowledge of existing diagnostic techniques allows an evidence-based strategy for diagnosis. New therapeutic choices may benefit patients with confirmed pulmonary embolism.

Key Words: Pulmonary embolism, D-dimer, CT angiogram, chest pain.

Introduction

PULMONARY EMBOLISM (PE) is one of the most enigmatic disease processes facing emergency medicine. Its high incidence, morbidity, and mortality are compounded by the difficulty of making the diagnosis. If syphilis is the “great masquerader,” then surely pulmonary embolism is the “great trickster.” It can present insidiously, eludes simplistic diagnostic strategies, and if not treated, can kill our patients. The importance of this clinical entity is reflected in the approximately 1,000 articles published each year, as well as ever-changing practice guidelines, which reflect advances in the relevant technology, assays, and medications.

Recently two major organizations, the American College of Emergency Physicians (ACEP) and the British Thoracic Society (BTS), separately revised guidelines for the evaluation and management of suspected pulmonary embolism (1, 2).

This article will concentrate on recent changes in the diagnosis of PE, as well as new treatment options for emergency department (ED) patients.

Epidemiology

The incidence of PE in the United States is estimated at 600,000 cases per year (3); it results in 50,000–200,000 deaths annually (4). Early estimates from the 1970s and 1980s suggest that roughly two-thirds of fatal PEs were undiagnosed until autopsy (3, 5). Short-term survival rates for PE were originally reported at 77–94% (6–9). One cohort study using data for 1966–1999 demonstrated a 59% thirty-day survival rate and 48% one-year survival rate for patients diagnosed with pulmonary embolism (10). Patients presenting with hypotension have had a higher initial mortality rate (up to 30%) (11) than do patients with co-morbidities such as congestive heart failure, malignancy, and neurological disease (10). However, Calder et al. in 2005 pointed out that much of this mortality data was overestimated, based on inpatient or autopsy populations, while analysis of untreated or missed pulmonary embolism in ambulatory patients treated in the ED had recurrence rates and mortality less than 5% (12).

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Glossary

ABG = arterial blood gas	LE = lower extremity
ACEP = American College of Emergency Physicians	LMWH = low-molecular-weight heparin
ACLS = advanced cardiac life support	LR = likelihood ratio
BTS = British Thoracic Society	MDA = trademark for a type of D-dimer
CT = computed tomography	PA = pulmonary artery (angiogram)
CTA = CT angiogram	PaCO ₂ = arterial partial pressure of carbon dioxide
CTV = CT venogram	PaO ₂ = arterial partial pressure of oxygen
D/C = discharge	PE = pulmonary embolism
DSA = digital subtraction angiography	PIOPED = Prospective Investigation of Pulmonary Embolism Diagnosis
DVT = deep venous thrombosis	TEE = transesophageal echo
Dx = diagnosis	V/Q = ventilation/perfusion
ED = emergency department	VTE = venous thromboembolism
ELISA = enzyme-linked immunosorbent assay	
JVD = jugular venous distention	

Pathophysiology

Pulmonary embolism is commonly a sequela of thrombosis of the deep veins of the legs or pelvis. Less commonly, the origin of the clot is the vena cava, an upper extremity, or even the hemorrhoidal vein. Approximately 70% of patients on diagnosis with PE have a proven deep venous thrombosis (DVT), and it is assumed that the other 30% have a DVT that has already been dislodged (13).

Risk factors for thrombosis, and consequent PE, include those associated with Virchow's triad: stasis, trauma, and hypercoagulability. The major risk factors are abdominal/pelvic surgery, hip/knee replacement, late pregnancy, c-section, lower limb fracture, abdomen/pelvis/advanced malignancy, immobility, as well as previous PE. Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED), a study validating the use of nuclear lung scanning with a pulmonary angiogram, provides excellent data on the clinical manifestations of PE (14). Fifty-six percent of patients with PE in the PIOPED study had immobility, making this the most common factor (14). Minor risk factors (Table 1) include congenital heart disease, congestive heart failure, hypertension, superficial venous thrombosis, indwelling venous catheters, chronic obstructive pulmonary disease, oral contraceptives/estrogen replacement therapy, neurologic disability, long distance travel and obesity (2). Increasing use of indwelling central catheters in the subclavian vein have made upper extremity DVTs more common than in the past, accounting for up to 20% of pulmonary embolisms in some studies (15, 16). Cigarette smoking is believed to be a minor risk factor, although

TABLE 1

Risk Factors for Pulmonary Embolism

Major Risk Factors for PE

Immobility
Abdominal/pelvic surgery
Hip/knee replacement
Late pregnancy
C-section
Lower limb fracture
Abdomen/pelvis/advanced malignancy
Previous PE

Minor Risk Factors for PE

Congenital heart disease
Congestive heart failure
Hypertension
Superficial venous thrombosis
Indwelling venous catheter
Chronic obstructive pulmonary disease
Oral contraceptives/estrogen therapy
Neurologic disability
Long-distance travel
Obesity
Smoking

Source: reference 2.

this was not confirmed in one recent study (17). When patients with PE are tested, thrombophilias such as Factor V Leiden, antiphospholipid antibody syndrome, and protein C and S deficiencies are present in 25–50% of patients with confirmed PE (18). It is important to note that multiple risk factors are often present in patients with pulmonary embolism; some of these risk factors may be synergistic. For example, Factor V Leiden increases the risks of thromboembolism by 3–5-fold, but combined with estrogen use it rises to 35-fold (2, 13, 18).

Diagnosis

The signs and symptoms of pulmonary embolism overlap with those of many other disorders, making it a challenge of when to include it in the differential diagnosis of patients presenting with a nonspecific complaint. Data from the PIOPED study demonstrate that over 97% of patients with confirmed PE had dyspnea, tachypnea, or chest pain. Therefore, at the minimum, it is prudent to consider PE in any patient with one of these manifestations without a clear alternative diagnosis.

The clinical manifestations of pulmonary embolism run the gamut of frank hypotension and respiratory instability to no signs or symptoms at all. Massive PEs may present in cardiac arrest, with syncope, or with enough right heart strain to cause elevations of troponin (19–22). However, the most common presenting symptom in any PE is dyspnea, which occurs in approximately 75% of patients, with sudden onset dyspnea having a higher predictive value (15, 23). Chest pain, usually pleuritic in nature, is the second most common symptom, reported in 66% of PIOPED patients (14). Other symptoms include cough, hemoptysis, syncope, palpitations, wheezing, and leg pain (24). Patients may also be relatively asymptomatic (25), especially younger, healthy adults (26).

Physical examination also reveals various signs in a patient with PE. Patients may have tachypnea, tachycardia, rales/wheezing, fever, S3

or 4, leg edema, or jugular venous distention (JVD) (15, 21). Tachypnea (>16 breaths/minute) is frequently identified as the most common sign of PE, with tachycardia (>100 beats/minute) as the next most common (Table 2). As many ED patients present with one of these two signs, their specificity for PE is limited. PE may also be associated with fever, with or without radiographic changes, and thus potentially misdiagnosed as pneumonia.

The ECG on presentation will most commonly show sinus tachycardia with non-specific ST/T wave changes (24). Incomplete right bundle branch block is also frequently seen (27). The classic S1Q3T3 is reported in only 20% of patients; though suggestive, it is certainly not pathognomonic, since it may be present in any patient with right heart strain of any etiology (28).

Risk Stratification

When PE is considered, systematic risk stratification should be performed to help decide which additional diagnostic tests to perform. Accurate identification of PE relies heavily on an estimation of the patient's risk, to specify any subsequent testing.

The most objective way to perform risk stratification is through the use of a clinical decision rule. There are three clinical decision rules, which have been validated for the ED population: the Wells Criteria (29), the Wicki Criteria (30) and the Charlotte (also known as Kline) Criteria (31).

TABLE 2
Symptoms and Physical Signs of PE

Common Symptoms in Patients with PE	Percentage of Patients with Symptom
Dyspnea	84%
Pleuritic chest pain	74%
Apprehension	59%
Cough	53%
Hemoptysis	30%
Sweating	27%
Non-pleuritic chest pain	14%
Common Physical Signs in Patients with PE	Percentage of Patients with Sign
Tachypnea > 16 breaths/min	92%
Rales	58%
Accentuated S2	53%
Tachycardia > 100 beats/min	44%
Fever > 37.8°C	43%
Diaphoresis	36%
S3 or S4 gallop	34%
Thrombophlebitis	32%
Lower extremity edema	24%
Cardiac murmur	23%
Cyanosis	19%

Wells Criteria for Pulmonary Embolism

The Wells Criteria decision rule consists of a point scoring method (Table 3). A score of 0-2 is interpreted as low risk, correlating with a probability of PE of 3.6%. A score of 3-6 is moderate risk with 20.5% probability of PE, while a score of greater than 6 points is high risk with a 66.7% probability of PE. One of the strengths of the Wells Criteria rule is that it relies only on the history and physical, requiring no ancillary testing for risk stratification. One problem with the Wells Criteria is the “alternate diagnosis less likely than PE” component. This component adds some degree of subjectivity to an otherwise objective rule. However, the Wells Criteria have been prospectively validated. When compared with the Wicki Criteria, the Wells Criteria showed moderate-to-substantial interrater agreement (32) and were found to reliably risk stratify pretest probability for patients with suspected PE (33).

Wicki Criteria

Unlike the Wells Criteria, the Wicki Criteria rely on ancillary testing in addition to signs and symptoms. Calculation of a Wicki score requires interpretation of both a chest radiograph and an arterial blood gas (Table 4). Scores of 0-4 are low risk with a 10% probability of PE, scores of 5-8 are moderate risk with a 38% probability of PE, and scores of 9-12 are high risk, correlating with an 81% probability.

When the predictive accuracy and concordance of the Wells and Wicki Criteria were compared (by members of the group that did the initial Wicki Criteria research), the two prediction rules

were found to have similar predictive accuracy for PE among ED patients. It can be argued that the Wells Criteria are quicker, easier, and more cost-effective as well as providing results similar to those of the Wicki Criteria. Although the ACEP has not formally endorsed an individual scoring system, the Wells Criteria have the lowest pretest probability in the low risk group and are the only criteria that the ACEP recommends for use with whole blood cell qualitative D-dimer.

Charlotte Criteria

The Charlotte Criteria rule was specifically developed to determine if a patient is at low enough risk of PE to allow for diagnostically definitive bedside testing (Table 5). It stratifies patients into low-risk or high-risk groups. Among low-risk patients, PE can presumptively be excluded by the use of a D-dimer assay. If two or more of these components are present, the patient is considered at high risk with a 40% probability of PE; these patients are considered at too great a risk to allow for bedside testing (31). The lower risk group was not further subdivided and had a 13.3% probability for PE. The Charlotte Criteria results have been prospectively validated in conjunction with a diagnostic algorithm; patients deemed negative for PE through the combined use of this decision rule and the algorithm had a less than 1% false negative rate (34). Recently, a modified Charlotte Criteria rule, which excluded pregnant patients, patients > 70 years of age and patients with symptoms for more than four days, yielded a 99.9% negative predictive value for pulmonary embolism in patients with low clinical suspicion of PE, when used in conjunction with an enzyme-linked immunosorbent

TABLE 3
Wells Criteria for Assessment of Pretest Probability of Pulmonary Embolism

Criteria	Points
1. Suspected DVT	3.0
2. An alternative diagnosis is less likely than PE	3.0
3. Heart rate > 100 beats/min	1.5
4. Immobilization or surgery in previous 4 weeks	1.5
5. Previous DVT/PE	1.5
6. Hemoptysis	1.0
7. Malignancy (on treatment or treated within past 6 months)	1.0

Score	Mean Probability of PE	% of Patients with This Score	Risk
< 2	3.6%	40%	low
2-6	20.5%	53%	medium
> 6	66.7%	7%	high

TABLE 4
Wicki Criteria for the Assessment of Pretest Probability for PE

Criteria	Points
Age 60–79	1
Age > 79	2
Prior DVT/PE	2
Recent surgery	3
Heart rate > 100 beats/min	1
PaCO ₂ < 36	2
PaCO ₂ = 36–39	1
PaO ₂ < 49	4
PaO ₂ = 49–60	3
PaO ₂ > 60–71	2
PaO ₂ > 71–82	1
Chest X-ray: plate-like atelectasis	1
Chest X-ray: elevation of hemidiaphragm	1

Score	Mean Probability of PE	% of Patients with This Score	Interpretation of Risk
0–4	10%	49%	low
5–8	38%	44%	moderate
9–12	81%	6%	high

Source: reference 30.

TABLE 5
Charlotte Criteria for Rapid Rule-out of Pulmonary Embolism Using D-Dimer and Alveolar Dead Space

If any two are present, patient is unsafe for rule-out of pulmonary embolism

1. Age greater than 50 years or heart rate greater than systolic blood pressure
2. Recent surgery (requiring anesthesia) in past 4 weeks
3. Unilateral leg swelling (asymmetry on visual examination)
4. Hemoptysis
5. Unexplained room air pulse oximetry < 95% (non-smoker, no asthma, no chronic obstructive pulmonary disease)

Source: reference 31.

assay D-dimer (35). The only patient with a missed diagnosis of PE in this study had a pneumothorax that was treated, and a positive D-dimer that was disregarded due to the alternate diagnosis (35).

Risk Stratification by Clinical Opinion

Clinicians may opt to perform risk stratification without the use of a decision rule. While the opinion of experienced clinicians has showed good correlation with objective criteria (36), it is difficult to know how true this may be for all emergency physicians. It may be preferable to use one of the clinical decision rules above and augment the yielded pretest probability with clinical judgment.

Risk stratification establishes a pretest probability which then drives further testing to establish a post-test probability: the post-test probability is then used to “rule in” or “rule out” the diagnosis of PE. While each clinician must determine which thresholds to use for this purpose, driving the post-test probability below 1.5–2% is generally considered acceptable in excluding the diagnosis of PE. A post-test probability of 80–90% is generally used for “ruling-in” the diagnosis.

The most obvious risk of missing the diagnosis is disease progression, with its inherent morbidity and mortality; not as widely considered are the risks of over-diagnosing this disorder. Patients falsely branded with a PE will be exposed to the risks of anticoagulation (37), will probably be misdiagnosed again when presenting to health care providers, and may encounter difficulties with life and health insurance.

Diagnostic Testing

Choosing which test to order first is often based on clinician preference and institutional availability. Arterial blood gas (ABG) and chest X-ray are two tests that are often ordered, but have little effect on post-test probabilities.

ABG

Many authors believe that an ABG should not be part of the routine PE workup, as studies have

shown it has a low sensitivity and specificity (38–40). The incidence of a completely normal ABG approaches 40% in younger and healthier patients (39). Sensitivity for the test increases when the criteria for a positive test are arterial partial pressure of carbon dioxide (PaCO_2) > 35, an arterial partial pressure of oxygen (PaO_2) < 80, or an A-a gradient > 20. However, since the negative likelihood ratio (LR) using this criterion is 0.9, the ABG result has little impact on the pretest probability (40). However, it is important to note again that the Wicki and Charlotte Criteria both use an ABG as a component in calculating their respective scores.

Chest Radiograph

While the chest X-ray in the investigation of PE can lead to an alternate diagnosis such as pneumothorax or pneumonia, it usually has abnormalities that are nonspecific and non-diagnostic. Classic signs such as peripheral oligemia (Westermark's sign) and pleural wedge based densities (Hampton's hump) occur in less than 20% of patients (41–43). Conversely, up to 80% of X-rays in PE can be interpreted as abnormal when signs resulting from modification of anatomic structures (descending pulmonary arteries, elevated diaphragmatic domes, heart shadow, peripheral vessels) are taken into consideration (23, 24, 41, 42). Other X-ray signs such as densities, infiltrates, and effusions are all common with PE. Atelectasis and the resulting elevation of a hemidiaphragm are the most common X-ray abnormalities (43).

D-dimer

D-dimer is a fibrin degradation product formed by the enzymatic activity of cross-linked fibrin polymers. D-dimer is thus present in venous thromboembolism, but may also be present in malignancy, pregnancy, myocardial infarction, disseminated intravascular coagulation, sickle cell disease, and during the postoperative period (44). D-dimer levels are also correlated with position and size of the PE, and are thus highly accurate markers for segmental PEs and less accurate for peripheral subsegmental PEs (45).

The function of the D-dimer assay in the work-up of PE is to lower the post-test probability of PE; therefore, a negative result is quite useful. A positive result rarely alters our clinical suspicion significantly and therefore necessitates further testing.

There are five different types of D-dimer assays available: enzyme-linked immunosorbent assay, whole blood agglutination, latex agglutination, and the newer turbidimetric and immunofiltration assays.

Each assay has different diagnostic characteristics, making generalizations of the entire class difficult.

Whole blood agglutination. The SimpliRED™ test, a qualitative red cell agglutination (whole blood assay) has been reported to have an overall sensitivity of 84.8% and a specificity of 68.4% in a 1,177 patient trial that assessed its effectiveness in diagnosing PE (46). This test is rapid and can be done in minutes, even at the bedside. It has been concluded by both the ACEP and the British Thoracic Society that this whole blood assay can indicate a sufficiently reduced risk of PE to rule out the diagnosis in a patient with low pretest probability as defined by Wells criteria (1, 2).

Enzyme-linked immunosorbent assay (ELISA). ELISA tests have shown a pooled sensitivity of 97% (47), but the conventional test may take up to 4 hours to run. In one study, a rapid ELISA test had an overall sensitivity of 95% (48) and one test in particular, the VIDAS™, has been shown to have a sensitivity of 97%, but a specificity as low as 8% (49). A negative result on this test has been specifically shown to be of value in both the low and intermediate probability groups (48).

Latex agglutination. Latex agglutination assays have shown disappointing results when used in the diagnosis of PE. They were designed for the diagnosis of hematologic disorders such as disseminated intravascular coagulation. Given this purpose, the sensitivity suffers to yield a greater specificity; the values are 70% and 76% respectively (1) and thus should not be used in the diagnosis of PE.

Immunoassays. Immunoassays, both immunofiltration and latex particle immunoassays, are new and promising. The MDA™ latex particle immunoassay has demonstrated sensitivities of 97–99% (49, 50).

Turbidimetric. The turbidimetric assays utilize another, newer form of D-dimer; these assays have shown a pooled sensitivity of > 95% (49), but take two hours to yield results.

The British Thoracic Society and the ACEP agree on a level B recommendation that D-dimer should only be considered after assessment of clinical probability, and that D-dimer cannot be used as a lone test to rule out PE in the high pretest probability cohort. The ACEP has assigned a level B recommendation for using a negative D-dimer to exclude PE in low Wells pretest probability patients with a negative whole blood assay (i.e., SimpliRED™). A level C recommendation was given for the use of the whole blood (SimpliRED™) assay without Wells Criteria. The British Thoracic Society agrees with the recommendation and recommends that SimpliRED™ be limited to low pretest probability groups, i.e., a Wells of less than three.

The ACEP gives a B recommendation for the use of a negative ELISA or turbidimetric D-dimer to rule out PE in the low risk groups only. The ACEP only gives a C recommendation for using the immunofiltration D-dimer because it is new and lacks the data of the other tests. However, BTS has taken the stance of a level B recommendation that any D-dimer in the low risk group can exclude PE, while the VIDAS and MDA D-dimers exclude PE in both low and intermediate risk groups. BTS further recommends that each hospital provide information on the sensitivity and specificity of its D-dimer test. Using the BTS guidelines, it is possible to rapidly rule out a PE in a patient even with intermediate pretest probability, if the hospital has the VIDAS or MDA tests (1, 2).

Alveolar Dead-Space Evaluation

As pulmonary emboli result in an obstruction of the vasculature without affecting airway patency, an increased physiologic dead-space would be expected. This can be quantified by comparing the arterial and expired carbon dioxide levels. The percentage of alveolar dead-space can be calculated by a modification of the Enghoff equation (51):

$$\text{Dead-Space Percent} = 100 \times (P_a\text{CO}_2 - P_{\text{et}}\text{CO}_2) / (P_a\text{CO}_2)$$

An abnormal result is generally considered >20%. End tidal CO₂ is available in many EDs at the bedside and can be used for this method, although in the studies analyzing the use of dead-space fraction, measurements were done by respiratory therapists with portable equipment and simultaneous drawing of arterial blood (52).

While this is not useful as a sole test, the combination of a D-dimer and a normal alveolar-dead space percentage may be more sensitive than a D-dimer alone. Kline et al. used this strategy, which yielded a false negative rate of less than 1% (53, 54).

Nuclear Isotope Lung Scanning— Ventilation/Perfusion (V/Q) Scan

In the past, ventilation/perfusion imaging was considered the diagnostic test of choice for the evaluation of PE. PIOPED established the accuracy of this test with a criterion standard of pulmonary angiogram. However, the use of the V/Q scan is problematic, primarily because its interpretation is hindered by multiple cutoffs, ranging from normal to high probability, each with its own diagnostic characteristics. While the PIOPED study established four levels of test reporting—normal, low probability, intermediate probability,

and high probability—the low and intermediate results should preferably be referred to as non-diagnostic. More than 60% of patients fell into this non-diagnostic category. In PIOPED, even when the scan was read as normal, there was still a 4% incidence of PE; similarly troubling, high probability scans were associated with a 12% false positive rate. However, other studies have shown that withholding anticoagulation from patients with a normal V/Q scan resulted in a less than 1% subsequent PE on long-term follow-up (55, 56).

The ACEP has made a level A recommendation that patients with low-to-moderate pretest probability and a normal V/Q scan can be deemed not to have a significant PE. However, if the same patients have a non-diagnostic V/Q scan, the ACEP's B level recommendation is that in order to exclude significant PE without going to pulmonary angiogram, the patient must have one of the following: a negative turbidimetric or ELISA assay, a negative whole blood D-dimer with a Wells score less than 4, negative bilateral ultrasound in low probability group only, or negative serial bilateral ultrasound for the moderate Wells score group. The BTS guidelines differ; with a level B recommendation they prefer that a V/Q scan be the initial investigation only if a chest radiograph is normal, there is no concurrent cardiopulmonary disease, standardized reporting criteria are used, and a non-diagnostic result is followed by further imaging. BTS also considers that a normal V/Q scan reliably excludes PE in low risk groups and in intermediate groups with a negative VIDAS™ or MDA™ D-dimer. Thus, while ACEP guidelines state that a V/Q scan cannot rule out PE in a high probability groups, the BTS guidelines conclude that a normal V/Q scan can only rule out PE in a high probability patient if it is read as normal AND the patient has a normal chest X-ray and no baseline cardiopulmonary disease. Otherwise, BTS states that the patient must go on to CT angiogram.

Leg Ultrasound

Doppler examination of the lower extremities can be used to establish the diagnosis of PE if the clinician accepts the proposition that the presence of DVT in a patient with symptoms suggestive of PE confirms a PE. Patients with confirmed PE will have DVT identified by leg ultrasound in approximately 50–70% of cases (14, 55). The treatment for stable PE and DVT is the same, so it may be valuable to use leg ultrasound as an initial test in stable patients with suspected venous thromboembolism (VTE) or after inconclusive imaging. Limiting the use of this test to patients with signs or

symptoms of DVT can increase the diagnostic yield. If the clinician has been trained and has the available equipment, a positive bedside ultrasound can quickly and accurately make the diagnosis of DVT and therefore PE (57).

Ultrasound also has implications for the possibility of recurrent PE. Theoretically, if diagnostic testing misses a PE, but there is no more clot to embolize, then the patient will not incur as significant a risk from the misdiagnosis. Serial leg imaging has been found to be useful with a 3-month venous thromboembolism (DVT or PE) rate of only 0.5% among patients with non-diagnostic V/Q scans and initial negative lower extremity Dopplers for DVT (58, 59), but such protocols require reliable patient follow-up and may have resource implications for repeat visits.

The ACEP supports using serial ultrasound for nondeterminate V/Q in low risk groups. BTS recommends the opposite use of ultrasound; a positive ultrasound in patients suspected of having a PE to confirm diagnosis. However, the BTS position is in agreement with the current literature and states that a single leg ultrasound should not be used for exclusion of subclinical DVT.

CT Angiogram

In many institutions, the spiral CT has become the initial diagnostic modality for PE, because of the high number of indeterminate studies obtained using conventional V/Q scans (14). The spiral CT, using as little as 100 cc of contrast, will directly visualize thromboembolic filling defects as well as pleural effusions, vascular remodeling, and oligemia, any of which may be present with PE (60). It is important to note that adequate visualization of the pulmonary vasculature cannot be accomplished with a standard CT scan of the chest; it requires dedicated imaging procedures and protocols often referred to as CT angiogram (CTA). Using CT angiogram as the initial imaging modality has proven to be cost effective (61).

Another advantage of the CTA is that it may reveal alternative diagnoses. A patient suspected of having PE may turn out to have pneumonia, aortic dissection, tumor or pneumothorax, all which can be revealed by the CTA (62).

Historically, the main limitation of spiral CT has been the inability to identify subsegmental PE (63). In the ACEP guidelines, it is noted that the sensitivity of spiral CT for large segmental emboli is greater than 95%, while for subsegmental emboli it is only 77%, according to three studies from 1996–1997 (64–66). A recent review of the spiral CT literature is much more promising (60). In 2000, Goodman

(67) showed a 1% rate of PE on follow-up after normal spiral CT. In 2002–2003, two retrospective and two prospective studies were published with enrollments of 993, 441, 507 and 246 respectively (68–71). The studies had a false negative rate of 0.9–1.2% and proved that patient outcome is not adversely affected by withholding anticoagulation on the basis of a good-quality, normal spiral CT.

In 1998, multidetector CT scanners became available; these scanners can image multiple slices with a single revolution of the detectors. Sixteen multidetector spiral CT scanners are now available (60, 72), with the number of detectors growing yearly. The multidetector scanners allow 1-mm to sub-millimeter resolution, and the data can be transformed into 2-D and 3-D reconstructed images. One of the most important features of this new technology is the ability to image the entire pulmonary vasculature in one breath-hold. As a result of these advantages, the multidetector scanners are able to significantly increase the detection of subsegmental PE and evaluate pulmonary vasculature down to 6th-order branches (73–75). PI-OPED II, a study of CT scanners for the diagnosis of PE, will further elaborate on the accuracy of the new-generation scanners and test their ability to scan for pelvis and thigh DVT while the patient is receiving the pulmonary scan (76). The latter strategy is referred to as “CT venogram” (CTV). Using the same contrast bolus as the CTA of the chest, DVTs can be detected from the pelvis all the way down to the calves. While it carries the downside of increased radiation dosing, this approach offers increased sensitivity. In a seven-center prospective trial, scanning the pelvis and legs above the knee identified an additional 18% of patients needing anticoagulation (77). However, it is important to note that this study was done in 1998–1999, when the first generation of multidetector CTs first became available (55), and the same machine was not used at all sites. It is possible that the new multidetector scanners would have found pulmonary embolisms in many of the patients who had the sole venogram diagnosis of DVT.

In response to the emerging data on CTA, the ACEP makes a level B recommendation that thin spiral CT with 1–2 mm image reconstruction may be used as an alternative to V/Q scan during the diagnostic evaluation of the patient with suspected PE, and a C recommendation to also perform CT venogram. The BTS guidelines place an even greater faith in the use of CTA for the diagnosis of PE. With a level B recommendation, they state that the CT pulmonary angiography is the recommended imaging modality for non-massive PE. Furthermore, BTS has stated that patients with a good quality CT

angiogram need no further investigation for PE regardless of the assigned level of pretest probability.

Echocardiography

Bedside echocardiography will demonstrate evidence of PE in up to 80% of cases (78), especially in unstable patients when transesophageal echo (TEE) is used (79). Intracardiac thrombi in the right heart may also be visualized. Echocardiography is especially useful for patients suspected of massive PE or unstable patients who cannot be moved safely outside of the ED. Furthermore, patients with right ventricular dysfunction may benefit from the administration of thrombolytic therapy.

Conventional Angiogram

The pulmonary angiogram was long considered ideal for diagnosis of PE. The test is no longer even available at some centers, and radiologists who were once facile with the process now perform and interpret these scans only rarely. Even when it was used commonly, there was a high rate of interobserver disagreement for subsegmental PEs (80). The test used today is often digital subtraction angiography (DSA); it is unknown whether the conventional angiography sensitivities are still applicable (81). The accuracy of the conventional pulmonary angiogram relies on selective catheterization of each subsegmental branch of the pulmonary vasculature. Angiography of only segmental branches, a common way of performing the exam, will lower the sensitivities (82).

The recurrence rate of pulmonary embolism in patients with normal angiograms ranges from 0.6–4.2% (83). Serious complications (from dye load, renal nephropathy and the invasive nature of the procedure) occur in 1.5% of cases, and a 0.5% procedural mortality rate has been reported (15). However, newer generation CT scanners appear to produce similar if not better results with less invasive risk. Data from PIOPED II will establish whether CTA should be the new criterion standard for pulmonary embolism.

Post-test Probability

After testing, a post-test probability can be generated. If this probability crosses the threshold for “ruling-in” or “ruling-out” the diagnosis of PE, then the evaluation is complete. However, if diagnostic uncertainty still exists, the patient will have to undergo further evaluation using the generated post-test probability as the new pretest probability. Whether this testing will take place in the ED, on

the inpatient ward, or at a later follow-up appointment depends on the individual clinical situation.

Treatment

While the diagnosis of PE is a true test of clinical acumen, the treatment is relatively straightforward. Countless review articles and monographs discuss the treatment regimens for venous thromboembolism (e.g., 12, 13, 25). Areas of new interest include the use of low-molecular-weight heparin and indications for the use of thrombolytics.

Low-Molecular-Weight Heparin

Anticoagulation must be administered to patients with confirmed PE. For unstable patients or those at high risk, anticoagulation is often administered empirically while the patient is undergoing further work-up. This may be achieved with equal efficacy by using either low-molecular-weight heparin (LMWH) or unfractionated heparin (84–86). Unfractionated heparin will have a quicker onset and, according to BTS, may be more desirable for massive PE or any situation in which anticoagulation may need reversal.

LMWH does not require monitoring of partial thromboplastin time (PTT), is accurately dosed on a per kilogram basis in a once or twice daily fashion, and is less likely to induce bleeding and thrombocytopenia. Low-molecular-weight heparins seem ideally suited to the environment of the ED when infusions require medication pumps and careful nursing care, and one subcutaneous injection allows twelve hours without any further treatment administration.

Low-molecular-weight heparins also offer the additional flexibility of treatment in the patient's home. For stable patients with confirmed pulmonary embolism, the strategy of discharge with follow-up and prescription for LMWH can be considered. At this point, the data is still accumulating, but this strategy may allow outpatient management of a disease that prior to now uniformly required hospital admission. Sending patients with non-diagnostic work-ups home on LMWH is also a tenable option. Patients would be able to stay on treatment until follow-up testing sufficiently lowers the possibility of PE. However, further studies must be performed before this strategy can be recommended.

Thrombolysis

If a massive PE causes circulatory collapse, early thrombolysis is recommended (87). One study in a controlled trial of thrombolysis versus heparin was aborted after 4 patients who were given thrombolytics lived while 4 patients given only heparin died

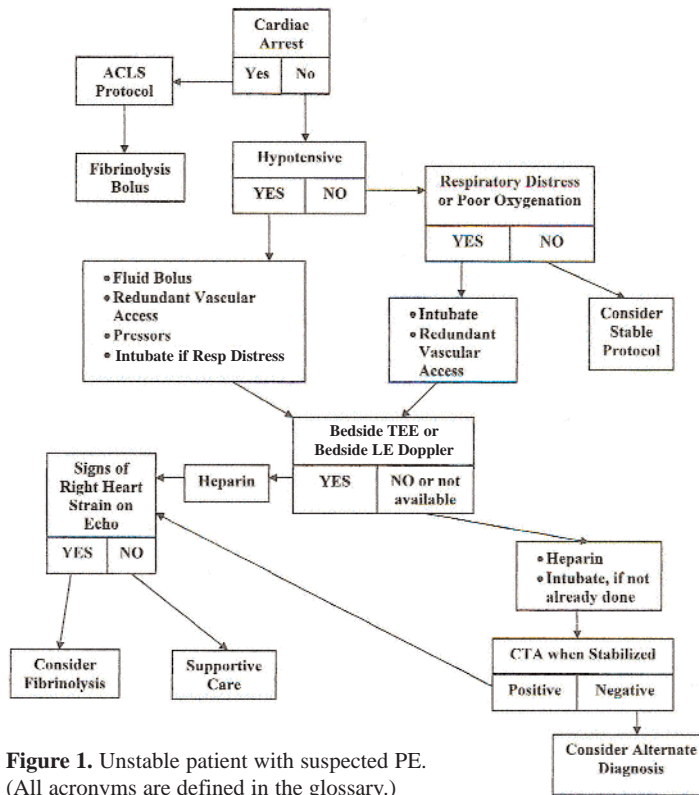


Figure 1. Unstable patient with suspected PE. (All acronyms are defined in the glossary.)

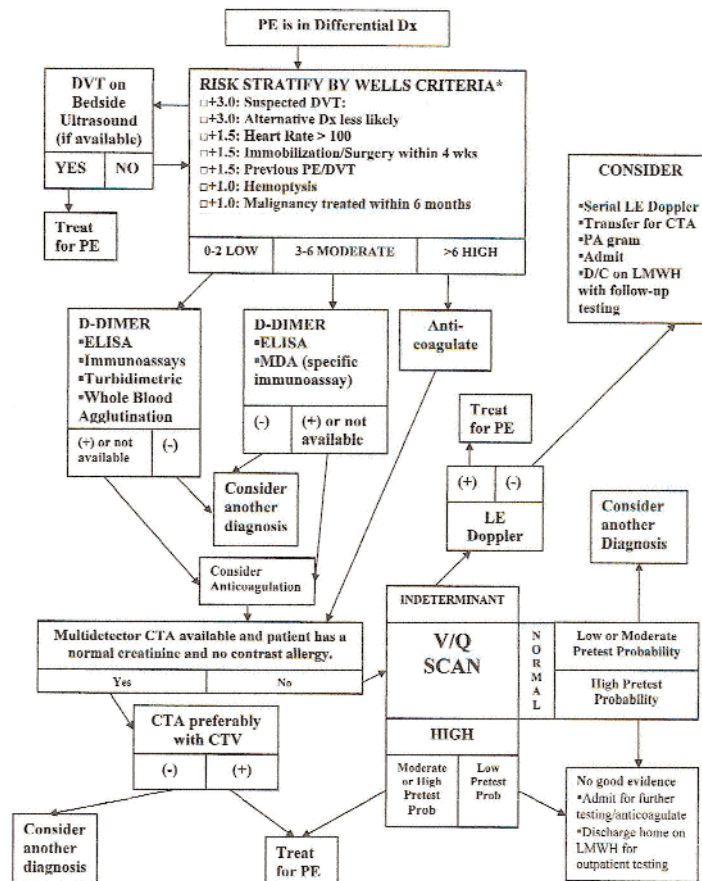


Figure 2. Stable patient with suspected PE. (All acronyms are defined in the glossary.)
 *May also use other objective criteria (Wicki or Kline)

Key Concepts

1. PE should be considered in any patient with unexplained dyspnea, tachypnea or chest pain. These patients must be risk stratified, ideally by a clinical decision rule.
2. A negative ELISA or MDA™ D-dimer will exclude PE in both low- and moderate-risk groups. Turbidimetric and SimpliRED™ D-dimers will exclude PE in low-risk groups. Latex agglutination D-dimers should not be used for excluding PE in any group. An alternative diagnosis should always be sought when PE is excluded.
3. CT angiogram (CTA) with a multidetector scanner is the initial imaging study for stable patients with suspected PE. For patients with low and moderate clinical pretest probability, a negative CTA excludes the diagnosis of PE.
4. V/Q scans should be used only when CTA is not available or contraindicated. All indeterminate scans should have a CTA or pulmonary angiogram done before PE is excluded.
5. Unfractionated heparin and low-molecular-weight heparin are both treatment options for patients with PE. In patients with confirmed PE and hypotension, thrombolytics should be administered if not contraindicated.

(88). Currently, clear data exist only for lysis in hypotensive patients (87–91). Debate is ongoing as to whether stable patients with right ventricle strain on echocardiogram should receive thrombolysis. Patients with right heart strain who received thrombolysis recovered right heart function more rapidly, but there was no demonstrated mortality benefit (92–95).

While the BTS supports a C recommendation of using alteplase (96) for fibrinolysis of PE because it does not worsen hypotension, currently the FDA has approved the use of streptokinase, urokinase or rt-PA for the treatment of pulmonary embolism. The ACEP gives a level B recommendation to considering thrombolytics in hemodynamically unstable patients with proven PE, and a C recommendation to the lysing of unstable patients with high clinical suspicion of PE. The ACEP also gives a level C recommendation for fibrinolysis of stable patients with confirmed PE and right ventricular dysfunction on echocardiography.

Conclusions

Diagnosis of PE may again change when the results of PIOPED II are published. In the interim, the ACEP clinical policy and BTS guidelines give an evidence-based roadmap to the evaluation and treatment of pulmonary embolism. The following are key points to the approach to pulmonary embolism in the emergency department:

1. We should consider PE in any patient with unexplained dyspnea, tachypnea, or chest pain.
2. All patients suspected of PE must be risk stratified, ideally by using criteria validated by a clinical decision rule.
3. If both PE and DVT are suspected and ultrasound is readily available, a positive leg ultrasound for DVT is sufficient for the di-

agnosis of pulmonary embolism, and treatment should be initiated.

4. If the VIDAS™ or MDA™ D-dimer is negative, PE may be excluded in the low- and moderate-risk groups. Other D-dimer assays (ELISA, turbidimetric, SimpliRED™) will reliably exclude PE in the low-risk group and no further imaging is warranted.
5. CT angiogram is the initial imaging study of choice for stable patients. In patients with low- and moderate-pretest probability, a negative CTA effectively excludes the diagnosis of pulmonary embolism.
6. V/Q scans should be used only when CT is not available or the patient has a contraindication to CT scans or intravenous contrast. If V/Q is normal, another diagnosis should be sought. Patients with indeterminate V/Q scans should have CT angiogram performed. Patients with indeterminate scans in the high probability group should receive CTA or pulmonary angiogram. Patients in the moderate- and low-risk groups with indeterminate scans can have PE excluded by serial leg ultrasounds.
7. Bedside echocardiography or hemodynamic status of the patient and CT angiogram are used diagnostically for suspected massive PE. If PE is confirmed, hypotensive patients should be given lysis. For hypotensive patients with high clinical suspicion of PE, thrombolytics can be considered.
8. Unfractionated heparin and low-molecular-weight heparin are both treatment options for patients with confirmed pulmonary embolism.
9. The diagnostic algorithms represented in Figs. 1 and 2 provide a stepwise approach to both

the stable and unstable patient with respect to the current data presented in this paper.

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