The Diagnosis of Acute Pulmonary Embolism

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Abstract

This paper reviews the most current literature on the diagnosis of pulmonary thromboembolism. The epidemiology and symptomology of this disorder, including common symptoms such as fever, chest pain, dyspnea, edema, and syncope, are reviewed. The utility of basic and easily available testing, such as electrocardiography and chest radiography, is evaluated. The literature on determining the pretest probability of venous thromboembolism with scoring systems, such as the Wells Score, the Geneva Scoring System, and the Pulmonary Embolism Rule Out Criteria, is appraised. As the evaluation of pulmonary embolism has evolved, multiple imaging techniques has been developed and studied. Ultrasonography, computed tomography with angiography, magnetic resonance angiography, ventilation perfusion lung scanning, and SPECT ventilation-perfusion lung imaging are discussed. In conclusion, the diagnosis of pulmonary embolism remains complicated. Clinical suspicion and stratification should guide a diagnostic strategy for the comprehensive evaluation and diagnosis of patients with this disorder.

Keywords: pulmonary embolism, deep venous thrombosis, diagnosis, CT angiography, ventilation-perfusion scans, clinical decision rules

Pulmonary embolism (PE) is a leading cause of morbidity and mortality in the United States, and between 5% and 10% of hospital deaths are attributable to PE.[1] From 1998 to 2005, the number of patients discharged from United States hospitals with a diagnosis of pulmonary embolism increased from 126,546 to 229,637.[1] Over this period, the hospital case fatality rate decreased from 12.3% to 8.2% ($p<0.001$).[1] The length of stay decreased, but hospital charges for these patients increased nearly 100% ($p<0.001$). In the United States, approximately 100,000 to 200,000 deaths occur in over 600,000 episodes of pulmonary embolism per year.[2-6] An overwhelming majority of these deaths occur when the disease is under-recognized or misdiagnosed and ultimately discovered on autopsy.[7,8] With the correct diagnosis and effective treatment, the risk of death diminishes dramatically.[9] As expected, patients who present with shock have the highest mortality from PE. Unfortunately, even with myriad diagnostic tests and treatment options available, PE is common, lethal, and underdiagnosed.[1,10]

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Pulmonary embolism can present along a spectrum from the asymptomatic individual incidentally diagnosed to the patient presenting with cardio-

genic shock.[11] Thus the diagnosis of acute PE is ultimately guided by the clinician's index of suspicion for the disease and augmented by diagnostic tests. PE is closely linked with deep venous thrombosis (DVT) and should be considered a different manifestation of the same disorder, namely venous thromboembolism (VTE). The recognition of the signs and symptoms of PE is the most important initial diagnostic step. A careful clinical history and physical examination is crucial to identify the patients at risk and to assess the pretest probability. In a review of the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED 1) data, Stein and Henry found that dyspnea was the most common symptom followed by pleuritic chest pain, cough, lower extremity edema, hemoptysis, palpitations, wheezing, and angina-like pain.[12] Pleuritic chest pain and hemoptysis are more common in patients with pulmonary infarction.[12] PE should always be considered in patients with chest pain, dyspnea, hemoptysis, syncope, and palpitations.[13] The possibility of PE can be subtle with non-specific symptoms and signs, such as tachycardia, tachypnea, and fever. In Stein's study, tachypnea was the most common physical examination finding followed by crackles, tachycardia, and an increased pulmonic heart tone.[12] Other examination findings in this study included evidence of DVT, fever> 38.5° C, diaphoresis, wheezing, and a pleural friction rub in 6% to 14% of patients.[12] Lower extremity signs, such as edema, leg and calf tenderness, erythema, venous cords, and Homan's sign, may indicate a DVT. Classically, 90% of emboli originate from proximal lower extremity DVT.[13] However, only 48.6% of patients with a high probability of PE had a DVT.[14] Upper extremity venous thrombosis and catheter-associated thromboses are additional sources of PE. Due to the nonspecific symptoms of PE and DVT, there can be substantial delays in seeking medical attention and diagnosis once medical attention is sought.[15]

Clinical suspicion and clinical decision rules

The diagnosis of PE and DVT is dependent upon the clinician's suspicion of the disease. Unfortunately, there are numerous studies that demonstrate failures or delays in diagnosis of PE. [2-6, 11] Further, the morbidity and mortality of VTE increase when the diagnosis is not made.[2-6] Paradoxically, as the evaluation for VTE has evolved, more patients are undergoing evaluation with imaging for PE, but the diagnostic yield of these tests can be as low as 3.1% in the absence of clinical prediction rules.[16] There are numerous risk factors for VTE, including age greater than forty, previous VTE, surgery requiring anesthesia for more than 30 minutes, prolonged immobilization, stroke, heart failure, malignancy, fractures of the long bones or pelvis, spinal cord injury, obesity, smoking, pregnancy, estrogen therapy, inflammatory bowel disease, and genetic or acquired thrombophilia. Renal failure, nephrotic syndrome, central venous catheterization, COPD, and long distance travel have also been identified as risk factors.[11] Hip/knee surgery/fracture and spinal cord injury carry the highest risk.

Risk stratification and pretest probability

Stratifying patients into low risk, moderate risk, or high risk categories can be performed either by empiric assessment and "gestalt" or by the use of structured clinical prediction rules.[17] Structured clinical prediction rules standardize the approach to pretest assessment of probability and remove the variability of clinical experience found in clinical practice. There are numerous clinical prediction scores, including the Wells Score, Simplified Wells Score, Geneva Score, Revised Geneva Score, Simplified Revised Geneva Score, Miniati Score for Likelihood of Pulmonary Embolism, the Charlotte Rule, and the Hyer Score.[18-24] The Wells Rules, Simplified Wells Rules, and the Geneva scores are frequently used in clinical trials and have the most validation from clinical studies.[18] The clinical prediction rules devised by Wells, et al. use a point based system based on historical factors, such as malignancy (1 point), hemoptysis (1 point), previous DVT/PE (1.5 points), immobilization or recent surgery (1.5 points), heart rate >100 beats/minute (1.5 points), clinical evidence of DVT (3 points), and absence of equally likely alternative diagnosis (3 points).[25] In this point system, low (<2 points), intermediate (2-6 points), and high probability (>6 points)

indicate pretest probability. The simplified Wells rules assigns one point for each criterion and establishes a cut point above and below 4 to distinguish between low pretest probability and intermediate or high pretest probability.[25] The Pulmonary Embolism Rule Out Criteria (PERC) has been proposed as a method to decrease testing in suspected pulmonary embolism. These criteria use a point system in which each criterion is valued at one point, and PE is ruled out if all of the criteria are negative. The PERC score includes the following criteria: age > 55 years, heart rate > 100 beats per minute, room air oxygen saturation < 95%, previous episode of VTE, exogenous estrogen, recent surgery, unilateral leg swelling, and hemoptysis. A recent retrospective study found an incidence of 0.5% in 1020 patients with a negative PERC score.[2]

TABLE 1: Wells scores for pretest probability calculation

Wells Criteria	Points	Simplified Wells	Points
Clinical Signs of DVT	3.0	Clinical Signs of DVT	1.0
Recent Surgery Immobilization	1.5	Recent Surgery Immobilization	1.0
Heart Rate>100 bpm	1.5	Heart Rate>100 bpm	1.0
Previous VTE	1.5	Previous VTE	1.0
Hemoptysis	1.0	Hemoptysis	1.0
Malignancy	1.0	Malignancy	1.0
Alternative Diagnosis less likely than PE	3.0	Alternative Diagnosis less likely than PE	1.0

3-level Wells Score: Low <2 points, Intermediate 2-6 points, high >6 points. 2-level Wells Score PE Unlikely ≤ 4 points PE likely > 4 points. Simplified Wells Score: PE unlikely ≤1 point, PE Likely >1 point. BPM=beats per minute, PE=pulmonary embolism, VTE=venous thromboembolism

TABLE 2: Geneva scores for pretest probability calculation

Revised Geneva	Points	Simp Rev Geneva	Points
Age >65 years	1.0	Age >65	1.0
Previous VTE	3.0	Previous VTE	1.0
Surgery or Fracture within 1 month	2.0	Surgery or Fracture within one month	1.0
Active Malignancy	2.0	Active Malignancy	1.0
Heart Rate 75-94 bpm	3.0	Heart Rate 75-94 bpm	1.0
Heart Rate>95 bpm	5.0	Heart rate >95 bpm	1.0
Unilateral Leg Pain	3.0	Unilateral leg pain	1.0
Hemoptysis	2.0	Hemoptysis	1.0
Pain on deep leg palpation	4.0	Pain on deep leg palpation	1.0

Revised Geneva Score: Low PTP 0-3 points, Intermediate PTP 4-10 points, High PTP >11 points. Simplified Revised Geneva Score: Low PTP 0-1 point, Intermediate 2-4 points, High 5 points or more.

Diagnostic testing

Electrocardiogram, chest radiographs, and selected laboratory tests

Routine initial diagnostic testing in the evaluation of a patient with symptoms suggestive of a PE is neither sensitive nor specific. Over the past twenty years, a bewildering number of diagnostic tests, either alone or in combination, has been studied as a means of excluding or confirming the diagnosis of PE. Arterial blood gas testing may demonstrate a respiratory alkalosis or hypoxemia, but arterial blood gas evaluation including the alveolar - arterial

gradient is neither sensitive nor specific.[12,27] The chest radiograph often demonstrates nonspecific findings; atelectasis (52-75%), pleural effusion (26-56%), pleural based opacities (23-36%), elevation of the diaphragm, cardiomegaly, and a normal radiograph can be seen.[12,13,28] A large international cooperative registry found that cardiomegaly on chest radiograph was the most common finding in pulmonary embolism followed by normal radiograph, pleural effusion, elevated diaphragm, atelectasis, and pulmonary artery enlargement.[29] The electrocardiogram (ECG) most commonly reveals sinus tachycardia or a normal electrocardiogram. The classic finding S1Q3T3 denotes right ventricular strain and is rarely seen in PE.[12,30,31] In Stein's evaluation of PIOPED 1, patients with PE had abnormal ECG between 39% of the time. The ECG was abnormal in 10% of patients who presented with isolated dyspnea compared to 54% of patients with pulmonary infarction and 80% of patients with circulatory collapse. The most common findings were nonspecific ST segment or T wave changes and were found in 44 % of patients.[12] Other ECG findings included sinus tachycardia, non-specific ST-T wave changes, and right bundle branch block.[12] Brain natriuretic peptide (BNP) levels are higher in patients with PE than those without PE; however, it is nonspecific and insensitive.[32] In a case-control study of patients with hemodynamically stable PE, BNP had a sensitivity of 60% and specificity of only 62%.[32] Serum troponin I and troponin T are elevated in PE, but are not useful in diagnosis.[33] They may be useful for risk stratification of patients with anatomically large PE.[33] Heart type fatty acid binding protein (H-FABP) is a highly sensitive marker for myocardial infarction that can be used as a predictor for outcome in acute PE.[34] The 30-day mortality for acute PE using the H-FABP had a 98% sensitivity and 77% specificity.[34]

D-dimer testing

The D-dimer is a cross-linked fibrin degradation product. It is elevated in active thrombosis and useful in identifying patients with possible PE. It has an excellent sensitivity in the evaluation of VTE but poor specificity. Conditions such as increasing age, malignancy, hospitalization, and previous DVT adversely affect the specificity of the D-dimer.[35,36] The different assays have a wide range in sensitivities.[25,37] The enzyme linked immunoabsorbent assay (ELISA) D-dimer is most useful in ruling out the diagnosis in outpatients who have a low pretest probability of PE.[37] In a large meta-analysis of over 7000 patients, the negative likelihood ratio of an ELISA (enzyme linked immunoabsorbent assay) was 0.13, and for a rapid ELISA it was 0.13.[38] In this analysis, whole blood and less sensitive qualitative assays had negative likelihood ratios that were not as useful in ruling out VTE.[38] D-dimer increases with age, reducing the ability to rule out PE in elderly patients with the cutoff value usually being 500 µg/L. However, a recent study with age adjusted D-dimer (patient's age multiplied by 10 if age greater than 50 years), PE could be ruled out in a larger number of patients.[39]

When combined with structured clinical decision rules, the D-dimer can be very useful in excluding the diagnosis of pulmonary embolism.[16,19,20,40-44] In patients who are at low risk based on the scoring systems listed above, the incidence of pulmonary embolism at three months in the setting of a negative highly sensitive D-dimer assay is extremely low.[37] The combination of the Wells rule plus a negative D-dimer carried a risk of VTE during a three month follow-up period of 0 -1.1% in two studies.[43,44] In general, intermediate and high-risk patients should receive diagnostic imaging.

Medical Imaging

Compression ultrasound

Compression ultrasound of the extremities is commonly used in the evaluation of VTE. It is readily available, has no radiographic contrast, and is non-invasive. The compression ultrasound has excellent sensitivity and specificity in symptomatic patients with proximal DVT. The estimated sensitivity is 89-96%, and the specificity is 94-99%.[41] In the evaluation of patients with suspected PE, a compression ultrasound is positive in 10-14% of patients when used as the initial diagnostic test.[45,46] When positive, it may limit the need for additional testing.[18] The yield of ultrasound

can be increased when the patient has symptoms or signs of proximal DVT. However, compression ultrasound cannot be used in isolation for the exclusion of PE as over 50% of patients with PE will have a negative ultrasound of the extremity veins.[46,47]

The anatomically based techniques used to image PE include ventilation and perfusion scintiphotography, contrast enhanced helical CT scanning, pulmonary angiography, echocardiography, and contrast-enhanced MRI. Each study has its own specific advantages and limitations.

Ventilation perfusion (V/Q) lung scanning

V/Q scanning was the imaging modality of choice until recent years. It is highly dependent on the baseline chest radiograph.[48] Indeterminate results were obtained in up to 54% of patients in one study.[49] A more recent study suggested that with the Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis (PISAPED) criteria the sensitivity of a PE-present scan (80.4%) and the specificity of a PE-absent scan (96.6%) were comparable to PIOPED data, but the number of non-diagnostic scans decreased from 20.6% using PIOPED criteria to 0% using PISAPED criteria.[50] V/Q scanning does not require iodinated contrast and has significantly lower radiation exposure than CT scanning.[49] As documented in the PIOPED 1 study, a normal V/Q scan virtually rules out a PE in the patient with a low to intermediate pre-test probability.[48] Patients with high clinical probability of PE and high probability V/Q scans had a 95% likelihood of having PE.[48] Patients with low clinical probability of PE and low probability V/Q scans had only a 4% likelihood of having PE. A recent prospective study demonstrated that a diagnostic protocol using clinical prediction rules and V/Q scanning has a high diagnostic yield when combined with compression ultrasound.[42] A diagnosis of VTE was established in 76% of patients and only 11% of patients required CT angiography.[42] V/Q scanning should be considered as first-line imaging with a normal chest radiograph, in pre-menopausal women, pregnant women, patients with renal insufficiency, and patients with contrast allergy.[19,48] A V/Q scan is still quite useful but may be less available due to the increasing use of CT scanning as the preferred choice in many centers. Single photon emission computed tomography (SPECT) is becoming more popular due to its ability to image in three dimensions as opposed to two dimensional imaging for lungs.[49] SPECT provides a more accurate size estimate and location of perfusion defects in subsegments.[48] With its higher image intensity contrast, it is more sensitive than planar perfusion scanning for identifying obstructed segments in chronic thromboembolic pulmonary hypertension.[50]

CT pulmonary angiography and venography

The advent of the multislice, multidetector CT scanner has made a substantial impact on the diagnosis of PE. The PIOPED II study compared multidetector CT angiogram (CTA) using 1.25 mm cuts with multidetector CTA with venography (CTA/CTV).[53] The sensitivity of CTA was 83% with a specificity of 96% for PE.[52] The sensitivity of CTA/CTV was 90%, and the specificity was 95%.[53] In PIOPED II, the number of nondiagnostic studies was 11%, and when pooled with other trials, non-diagnostic studies occurred in 6% of patients.[19,53] The CT PIOPED II study demonstrated excellent negative predictive value (99.1%) and had good positive predictive value.[53] CTV did not significantly alter posttest probability.[53] It is clear from this study that the concept of pretest probability is still necessary in the assessment for PE.[53] Most centers do not use combination CTA and CTV, and we are often forced to use duplex ultrasonography to augment the negative CT to rule out a significant PE for patients with high pretest likelihood of VTE.[19,53] The CTA also has the benefit of evaluating lymph nodes and the lung parenchyma. The crucial disadvantages include the need to obtain high quality scans with well timed boluses of contrast to obtain an optimal scan and the use of intravenous contrast. Iodinated contrast can cause renal dysfunction and allergic reactions. CTA typically uses more contrast than standard pulmonary angiography. The use of CT scans has increased at an average of rate of 28.1% per year, and this, of course, increases radiation exposure to patients.[54] Exposure to five to six chest CT scans is equivalent to an effective dose in atomic bomb

survivors of 40mSv. The most cancer susceptible organs are thyroid, breast, and lungs; the exposures from CTA scans is 100 to 400 times more than a two view chest radiograph.[55]

Pulmonary angiography

Pulmonary angiography is considered the standard imaging procedure but in general has fallen out of use in most centers due to its perceived risks and the increased use of CT scanning.[56] It carries a significant risk in patients with acute PE.[57] Moreover, in comparison to studies with CTA, it appears to have a lower sensitivity than CTA.[56, 58-60]

Magnetic resonance imaging

PIOPED III was a multicenter study designed to assess the sensitivity and specificity of magnetic resonance angiography (MRA) alone or with magnetic resonance venography for diagnosing pulmonary embolus. Unfortunately, MRA was technically inadequate in 25% of patients.[61] In patients with technically adequate images, MRA was 78% sensitive and 99% specific.[61] However, MRA should be considered only at centers that routinely perform the study and perform it well due to the difficulties in obtaining technically adequate images. MRA should be considered experimental at present.[9,61] MRI lacks the resolution, wider availability, and larger clinical experience that CT has attained.[60] As technology advances, the diagnostic value of each test is likely to evolve.

Thoracic ultrasound

Multiorgan ultrasonography has also become popular since it decreases the radiation and contrast associated with multidetector CTA. In a multicenter, prospective trial, Nazerian, et al. showed that lung, heart, and leg ultrasound along with D-dimer assays improved the accuracy of diagnosing PE. In addition, it is a quick tool that can be used at the beside in unstable patients.[62] Ultrasound was considered positive and diagnostic of PE if the sonographers were able to detect subpleural infarcts in the lung, right ventricular dilatation, thrombi in the heart, or the absence of total vein collapse during compression for DVT.[62] The presence of PE was confirmed by multidetector CTA in this study. Multiorgan sonography had a 90% sensitivity (higher than any individual sonography) and 86.2% specificity.[62]

Echocardiography

Transthoracic echocardiogram is often used to assess chest pain. In acute PE, the echocardiogram is useful to stratify hemodynamically stable patients to determine which patient is at risk for a poor outcome.[63-65] However, its use in an acute setting is sometimes limited by availability, cost, and interobserver variability in the interpretation of results. The findings of right ventricular dilatation and pulmonary hypertension are poor markers for increased mortality.[63-65] The echocardiogram may show evidence of

TABLE 3: Studies currently capable of EXCLUDING the diagnosis of embolism at different levels of clinical probability

	Low Clinical Probability	**Intermediate Clinical Probability**	**High Clinical Probability**
Elisa D-dimer	Negative	Negative	----------
Ventilation/Perfusion Scan	Normal or low probability	Normal	Normal
Computed Tomography	Normal	Normal	----------
Contrast Angiography	Normal	Normal	Normal

TABLE 4: Studies currently capable of CONFIRMING the diagnosis of embolism at different levels of clinical probability

	Low Clinical Probability	Intermediate Clinical Probability	High Clinical Probability
Elisa D-dimer	----------	----------	----------
Duplex Ultrasound	Positive	Positive	Positive
Ventilation/Perfusion Scan	----------	High Probability	High Probability
Computed Tomography	Positive	Positive	Positive
Contrast Angiography	Positive	Positive	Positive

right ventricular strain or overload. In addition, the echocardiogram is often used to identify patients at risk for the development of hemodynamic decompensation.[63-65] Transesophageal echocardiography can image the proximal pulmonary arteries and confirm a diagnosis of proximal massive PE, but it is unable to visualize the intermediate branches of the pulmonary artery.[64]

Summary

Multiple tests are available to aid in the diagnosis of pulmonary embolus. The diagnosis of PE is guided by suspicion for the disease. The classic signs and symptoms of DVT and PE and the risk factors for VTE are well known. The different clinical prediction models available help stratify risk and demonstrate the broad spectrum of VTE presentations. Interpretation of the diagnostic testing procedures should be guided by the clinical probability for the presence of PE. It is important to definitively rule out the diagnosis in the stable outpatient, but it is equally important to make this diagnosis in patients in cardiogenic shock with massive PE. Multiple diagnostic tests and evaluations may be required for assessment of PE. We must remain vigilant in our efforts to diagnose and treat this deadly disorder.

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