Review Article

Diagnosing pulmonary embolism

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Abstract

Pulmonary embolism (PE) is a common, treatable, highly lethal emergency, which despite advances in diagnostic testing, remains an under diagnosed killer. The mortality rate of diagnosed and treated pulmonary embolism ranges from 3-8%, but increases to about 30% in untreated pulmonary embolism. PE is a part of the spectrum of venousthromboembolic disease and most pulmonary emboli have their origin from clots in the iliac, deep femoral, or popliteal veins. Nonspecific clinical signs and symptoms with low sensitivity and specificity of routine tests such as arterial blood gas, chest roentgenogram and electrocardiogram make the diagnosis of PE very challenging for the clinician. Pulmonary angiography is the gold standard diagnostic test, but this technique is invasive, expensive, not readily available and labor intensive. Diagnostic strategies have revolved around establishing clinical probabilities based on predictive models, then ruling in or ruling out the diagnosis of PE with various tests. The aim of this article was to review the literature and present an evidence- based medicine approach to diagnosis of pulmonary embolism.

Key words: Duplex ultrasound, computed tomography, pulmonary angiogram, pulmonary embolism, ventilation perfusion scan

Introduction

Pulmonary embolism (PE) is a common, treatable, highly lethal emergency, which despite advances in diagnostic testing, remains an under diagnosed killer. PE is currently the third leading cause of death in the United States, with 50,000 to 100,000 estimated deaths per year and an incidence of 0.5 to 1 per 1000.[1,2] Studies in the Indian subcontinent show a low incidence of Venousthroembolism (VTE).[3,4] The mortality rate of diagnosed and treated pulmonary embolism ranges from 3-8%, but increases to about 30% in untreated pulmonary embolism.[5,6] PE is a part of the spectrum of venousthromboembolic disease and most pulmonary emboli have their origin from clots in the iliac, deep femoral, or popliteal veins. Non-specific clinical signs and symptoms with low sensitivity and specificity of routine tests such as arterial blood gas (ABG), chest roentgenogram (CXR) and electrocardiogram (ECG) make the diagnosis of PE very challenging for the clinician. Pulmonary angiography (PA) is the gold standard diagnostic test, but this technique is invasive, expensive, not readily available and labor intensive. Diagnostic strategies have revolved around establishing clinical probabilities based on predictive models, then ruling in or ruling out the diagnosis of PE with various tests. The aim of this article was to review the literature and present an evidence- based medicine approach to diagnosis of pulmonary embolism.

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Clinical Assessment

The clinical manifestation of PE such as dyspnea, hemoptysis, chest pain, hypoxemia, pulmonary infiltrate, etc are non specific and overlap with other cardiopulmonary diseases. Over the last decade, the

focus has been on developing predictive models based on combination of these variables in order to determine the pre-test probability of VTE disease.

Wells *et al*[7] developed a clinical model by reviewing the literature for well established risk factors, signs, symptoms and alternative diagnosis and came up with a scoring system. They classified the patients as having low, intermediate, or high probability for PE, based on their scoring system. They subsequently simplified their model to consist of the following seven criteria:[8] (1) clinical signs and symptoms of deep venous thrombosis (+3.0); (2) an alternative diagnosis that is less likely than pulmonary embolism (+3.0); (3) pulse rate greater than 100 beats/min (+1.5); (4) immobilization or surgery in the previous 4 weeks (+1.5); (5) previous deep venous thrombosis/pulmonary embolism (+1.5); (6) hemoptysis (+1.0); and (7) malignancy (on treatment, treated in the past 6 months, or palliative; +1.0). Summation of these point values can be trichotomized into low (<2), moderate (2 to 6), or high (>6) pretest probability, or further simplified to PE unlikely with scores ≤ 4.0 and PE likely if the score was > 4.0.There are other predictive models,[9] that have been developed to calculate the likelihood of PE.

In conclusion, clinical prediction models guide by providing an estimate of the probability of PE, thus promoting efficient use of resources and reducing unnecessary exposure to potentially harmful drugs such as anticoagulants.

D-dimer Assays

D-dimer is a degradation product released into the blood circulation when cross-linked fibrin undergoes endogenous fibrinolysis. The value of a positive D-dimer test is limited, as the levels are known to increase in conditions such as infection, trauma, inflammation, malignancy, surgery etc.[10] The clinical utility decreases in patient populations, where these conditions are seen frequently. Over the last three decades, there have been a number of clinical studies performed using either an ELISA or a latex agglutination assay for D-dimer, to exclude the diagnosis of venous thromboembolic disease.[11] These assays differ in sensitivity, specificity and likelihood ratios, among patients with suspected DVT or PE.

A systematic review of the literature to assess the sensitivity and specificity of the D-dimer assays and the variability of those measures among studies for diagnosing DVT and PE, was performed by Stein and colleagues.[11] In ranking the various assays according to sensitivity values and likelihood of increasing certainty for ruling out DVT or PE, the ELISA and quantitative rapid ELISA assay showed dominant values. The sensitivity values of these assays were clinically and statistically superior to the latex agglutination assays and showed less variability in those with suspected DVT or PE. The low negative likelihood ratio values of these assays compare favorably with the negative likelihood ratio for a normal to near normal ventilation perfusion (V/Q) scan, in patients with suspected PE and to negative lower extremity duplex ultrasonography in patients with suspected DVT. The specificity and positive likelihood ratio values varied amongst assays, but all were within a range considered to be of little clinical values in changing the pre-test to post-test probability of VTE. They concluded that the ELISAs (particularly the quantitative rapid ELISA) performed the best amongst the various D-dimer assays and a negative result, is as diagnostically useful as a normal lung scan or negative duplex ultrasonography for excluding VTE.

The potential for a blood test to exclude VTE has been received enthusiastically by clinicians eager to avoid expensive diagnostic testing, leading to widespread use of D-dimer testing.[12,13] Concern of false negative tests in unselected hospitalized patient population and the elderly, has been raised by some studies. Brotman and colleagues[14] performed a study in hospitalized patients to see how often false negative tests were seen in this population. They reported that Nineteen (42%) of the 45 patients with thrombosis had a negative D-dimer assay by at least one method.

A D-dimer value of ≤ 500 ng/L has been suggested as a universal cut-off by ELISA assay.[15] The cutoff levels for a given D-dimer assay cannot be extrapolated to other assays. Optimal cutoff values for some assays are as low as 40 ng/mL, but may be >500 ng/mL for other ELISAs.[16]

In conclusion, clinicians should be aware of the performance characteristics of the D-dimer assay being used in their laboratories. A low clinical pre-test probability, a negative D-dimer test by an ELISA assay in a symptomatic outpatient, can be useful in “ruling out”

the diagnosis of VTE.[17]

Ventilation - Perfusion Scan

V/Q is a frequently used test to establish the diagnosis of PE. It is based on identifying areas of ventilation without perfusion (mismatched defects) and is classified as high probability, intermediate probability, low probability and normal scan. The prospective investigation of pulmonary embolism diagnosis (PIOPED)[18] study was designed to study the sensitivity and specificity of the V/Q scan in patients suspected of having PE. In patient with high probability lung scans, 87% had angiographically proven PE, while < 4% with normal or near normal lung scans had clinically significant PE. But majority of the lung scans in the study were either intermediated probability (39%) or low probability (34%) and the angiographically proven diagnosis of PE was much lower in these groups, 33 and 16%, respectively. Interpretation of the V/Q scan can vary as there are different grading algorithms (PIOPED criteria, modified PIOPED criteria, McMaster Clinical criteria and PisaPED criteria and it is reader dependent and requires experience.[19] False negative scans can occur if there is a single embolus, small embolus, partially occlusive emboli, obstructive lung disease and diffuse parenchymal disease. False positive scans can occur due to adenopathy, vasculitis, emboli other than thrombi, mediastinitis and congenital abnormalities. In mechanically ventilated patients, performing and interpreting a V/Q scan can be challenging as breath holding, deep breathing and upright position are required to perform the ventilation scan. It is recommended that perfusion scan be performed first and if no perfusion defect is seen, then it obviates the need for a ventilation scan. Adding pre-test probability to the diagnostic equation, as in the PIOPED study, improves the performance of the V/Q scan.

In conclusion, a high probability lung scan result can be used to “rule in” the diagnosis of PE, whereas a normal scan rules out clinically significant PE. Any other scan result should be considered to be non-diagnostic and should be followed by further tests such as spiral CT or pulmonary angiography.

Echocardiography

Right ventricular (RV) failure and RV ischemia are the primary etiology by which early death from acute pulmonary embolism (APE) occurs. Although acute severe right ventricular dysfunction (RVD) can be detected by physical examination**,** echocardiography is a sensitive tool for diagnosing acute RVD in APE.[20] Hemodynamic instability defined as hypotension on presentation, has traditionally been used as the clinical discriminator between massive and non-massive APE and as a guide to recommend the use of thrombolytic therapy. Despite the lack of convincing data using survival as an end point in the unstable patient with APE,[21,22] thrombolytic therapy is often recommended for the hemodynamically stable patient who demonstrates RVD on echocardiogram.[23,24] Up to 30 to 50% of normotensive patients presenting with APE are found to have RVD by transthoracic echocardiographic assessment.[25]

As far as making a diagnosis of PE with transthoracic or transoesophageal echocardiography is concerned, the sensitivity for direct visualization of thromboemboli at any specific location within the pulmonary circulation is low.[26-28] Echocardiography can detect right heart hemodynamic changes, that indirectly suggests pulmonary embolism. Echocardiographic signs of RVD in APE include RV end-diastolic diameter without RV hypertrophy > 27 mm, RV/LV end diastolic ratio > 0.83, RV hypokinesis (with sparing of the apex), TR velocity > 2.7 m/s, pulmonary artery dilatation, lack of decreased inspiratory collapse of IVC, paradoxic systolic septal motion, etc. In patients with underlying cardiopulmonary disorders, the reliability of echocardiography for detecting RVD secondary to PE, decreases.

In conclusion, the limited specificity with the transthoracic approach, the invasiveness of the transesophageal approach and the low sensitivity with both approaches, makes echocardiography not a suitable routine diagnostic test for pulmonary embolism. It is useful to detect RVD in patients suspected of having APE and to rule out any other cardiac cause for the clinical presentation. The use of echocardiography can be individualized to unstable patients suspected of APE in the emergency room setting, or critically ill patients in intensive care unit.

Duplex Ultrasound

Duplex ultrasound (DU) is widely used to diagnose deep vein thrombosis (DVT) because of its safety,

availability, reliability and noninvasive nature. It combines real-time B-mode imaging, where failure of veins to compress is used as indirect evidence of the presence of thrombus and color Doppler, which assesses the presence of flow within the vessel. The sensitivity and specificity of DU for symptomatic proximal DVT range from 93 to 100% and 97 to 100%, respectively.[29,30] DU is operator dependent and can be technically difficult in obese patients, or patients with significant lower extremity edema. It has poor sensitivity in the diagnosis of calf vein and pelvic vein DVT. Acute and chronic thrombi look similar on DU and it cannot differentiate between the two.

DU has virtually replaced contrast venography as the diagnostic test of choice for DVT, even though the latter is considered the gold standard with the ability to assess proximal and distal venous system. Invasiveness, need for contrast and high yield of DU are responsible for the decline of venography.

PE and DVT are thought to represent two clinical manifestations of the same disease process and it is known that approximately 90% of symptomatic pulmonary emboli arise from thrombi located in the leg veins.[30] The prevalence of detectable DVT in patients with symptomatic PE has not been widely investigated and varies greatly among studies.[31,32] The site of the DVT does not seem to be as important as previously was thought, because PE can occur from any site of DVT formation. Calf vein thrombosis, previously considered relatively benign, propagates above the knee in approximately 25% cases and may cause PE without first extending proximally.[33] Likewise, although superficial thrombophlebitis is generally benign, it can extend into the deep venous system and pose a risk for PE. DU is insensitive for distal DVT which can result in significant PE and therefore a negative DU may not be enough to rule out DVT. A repeat DU is recommended by some within 3-14 days and this strategy has shown to reduce the risk of VTE to less than 2% in six months.[34] Diagnosing DVT in patients with suspected PE may obviate the need for further testing, because the treatment of DVT with and without associated PE is essentially the same.

In conclusion, DU has a role in assessing patients suspected of having PE. Since it is a rapid, non-invasive, low cost test which can be performed at the bedside, it is of value in critically ill intensive care unit patients, or as an initial test in the emergency room. It is of value in patients with a non diagnostic V/Q scan, a positive test will obviate the need for furher diagnostic tests and a negative test with low clinical probability for PE can be used to exclude the diagnosis of PE.

Pulmonary Angiogram

PA is generally considered to be the most definitive test for the diagnosis of PE. The presence of an intravascular filing defect is considered positive for diagnosing PE. As a result of limited availability, expense and expertise required to perform the test, it is not used routinely to diagnose PE. Clinicians too underutilize this test, as they are concerned about adverse effects such as reaction to the contrast, arrhythmias, hypotension etc. Data clearly shows that PA is a safe test with morbidity and mortality of about 1 and 0.5% respectively and patients with poor cardiopulmonary reserve have a slightly greater risk.[35] About 1% of the patients with normal pulmonary angiograms have an episode of symptomatic VTE during the next six months. The accuracy of pulmonary angiography for subsegmental PE has been questioned, but the clinical significance of subsegmental PE is not known.

In conclusion, PA is currently the gold standard test to diagnose PE. When there is a moderate to high clinical suspicion for PE and all other tests have been non-diagnostic, clinicians should consider PA, if available at their institution, as it is a definitive test for PE with low morbidity and mortality associated with it.

Computed Tomography

Helical computed tomography (CT) is rapidly becoming the test of choice to diagnose PE. It has virtually replaced V/Q scans and has almost eliminated the need for PA in the diagnostic algorithm. CT scan is a rapid, non-invasive, safe and a widely available test which provides significant additional information in patients with cardiopulmonary symptoms. There has been significant advances in CT scan technology, from conventional CT scans with long scan times, to single detector scan to multiple detector (4, 8, 16, 64 row) scans. This has resulted in faster imaging acquisition speed with the ability to scan the entire chest in a single breath hold, decreasing respiratory motion artifact. The scans are of

thinner collimation (0.6 to 1.25 mm), improving image quality, visualization of peripheral pulmonary arteries and interobserver agreement.

After invention of helical CT, the first study evaluating its use in PE came from Remy-Jardin *et al* in 1992.[36] In this study, researchers found a sensitivity of 100% and specificity of 96% for evaluation of the main, lobar and segmental vessels, when compared with PA. Further studies in which sub-segmental arteries were evaluated, showed lower sensitivity and specificity. Since the development of multi detector scans, the visualization of the peripheral arteries has improved significantly.[37,38] A major problem in the determination of sensitivity and specificity of CT pulmonary angiography is the use of conventional pulmonary angiography as the gold standard. The PIOPED study showed that the interobserver agreement for conventional pulmonary angiography at the lobar and segmental levels was excellent. However, there was high interobserver disagreement in assessment of sub-segmental PE. Thus, both CT angiography and conventional angiography have only modest accuracy and interobserver agreement at the sub-segmental level. The clinical significance of isolated sub-segmental PE is also uncertain. There are no historical data about the need to treat patients with isolated sub-segmental PE.[39,40]

Outcome studies have been performed to gauge if the negative predictive value of CT pulmonary angiography was reliable enough to withhold anticoagulation. They have shown that in a 3-12 month follow up period, the rate of PE/DVT is 0.2-0.5%, and this is the same, or lower, than the recurrence rate reported for conventional PA.

The introduction of CT venography has made CT a single convenient test to diagnose DVT and PE, at no additional cost or inconvenience to the patient. It also has the added advantage of visualizing the pelvic veins to diagnose DVT.

In conclusion, multi detector CT scan has a sensitivity and specificity comparable to PA in diagnosing PE. CT venography can be utilized at the same time to diagnose DVT. A positive scan can safely be used to “rule in” a diagnosis of PE. For a negative result, the clinician needs to factor in the clinical probability of PE, CT technology at their local site and other diagnostic tests in the evaluation of PE. But one can safely say that the newer multi detector CT scans have a negative predictive value comparable to PA and a negative result from a multi detector scan can be used to “rule out” the diagnosis of PE.

Magnetic Resonance Angiography

Diagnostic testing for PE has evolved over the last few decades with the development of new tests, their continuous assessment and refinement. Magnetic resonance angiography (MRA) is one of the newer diagnostic tests being evaluated for diagnosing PE. Gadolinium enhanced MRA has shown better results compared to non-contrast MRA in diagnosing PE and can be used to image the veins of the pelvis, lower extremities and the pulmonary arteries in the same setting.[41] MRA technology continues to improve and currently insufficient data with limited availability makes it difficult to recommend a place for gadolinium-enhanced MRA in the diagnostic pathway for PE. It may have use in patients with a strong suspicion of PE, in whom the results of other tests are equivocal and radiographic contrast material or ionizing radiation are relatively contraindicated.

Conclusion

PE is a lethal disease and there are arrays of diagnostic tests available to help evaluate patients suspected of PE. Clinicians should be aware of the accuracy and limitations of each test. Diagnostic algorithms[42] have been suggested by various authors and it may be helpful to refer to one for a diagnostic strategy.

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