CHAPTER

69

Pulmonary Embolism – Newer Concepts and Role of Thrombolysis

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Introduction

Pulmonary embolism (PE) is a common cardiovascular and cardiopulmonary illness with an incidence in the United States that exceeds 1 per 1000 and a mortality rate > 15% in the first 3 months after diagnosis.[1] Evidence of leg DVT is found in about 70% of patients who have sustained a pulmonary embolism.[2] Conversely, pulmonary embolism occurs in up to 50% of patients with proximal DVT of the legs (in the popliteal and/or more proximal veins), and is less likely when the thrombus is confined to the calf veins.[2]

Venous thromboembolism (VTE) is often overlooked as a major public health problem and viewed as a complication of hospitalization for another illness rather than as a specific disease entity. The potential public health benefit of preventing VTE is substantial: Data from randomized trials involving general surgical patients suggest that adequate prophylaxis in high-risk patients can prevent VTE in 1 of 10 patients and save the life of ~1 of 200 patients.[3]

Clinical Presentation

As both the extent and duration of embolic obstruction vary widely, pulmonary embolism can produce widely differing clinical pictures. From the point of view of treatment strategy and clinical outcome pulmonary embolism can be broadly divided in three categories.[2]

Acute minor pulmonary embolism

A small embolus often produces no symptoms. At the most patient may have dyspnea on exertion. Sometimes, patients present with complication of pulmonary infarction like chest pain, hemoptysis and fever.

Acute massive pulmonary embolism

When > 50% of the pulmonary circulation is suddenly obstructed, there is a substantial increase in right ventricular afterload and, it may result in high pulmonary artery pressure, right ventricular dysfunction, right heart failure and systemic hypotension.

Subacute massive pulmonary embolism

This is caused by multiple small or moderately sized emboli that accumulate over several weeks. The rises in the right ventricular end diastolic and right atrial pressures are of a lesser extent than in acute massive pulmonary embolism since there is time for adaptation to occur and the degree of right ventricular failure is less for a given degree of pulmonary artery obstruction. The main symptoms are increasing dyspnea and falling exercise tolerance. Patient usually remains hemodynamically stable. In advanced cases, cardiac output falls and frank

right heart failure develops. A further pulmonary embolus may change the picture to that resembling acute massive pulmonary embolism.[4]

Diagnostic Procedures

Electrocardiography

The main value of electrocardiography is in excluding other potential diagnoses, such as myocardial infarction or pericarditis. In minor pulmonary embolism there is no real hemodynamic stress and thus the only finding is sinus tachycardia. In massive pulmonary embolism, evidence of right heart strain may be seen (rightward shift of the QRS axis, transient right bundle branch block, Qr pattern in V1, T-wave inversion in leads V1–3, SI QIII TIII pattern, P pulmonale), but these signs are non-specific.[5]

Echocardiography

In massive pulmonary embolism the right ventricle is dilated and hypokinetic, with abnormal motion of the interventricular septum. However, because the right ventricle may show no dysfunction even in patients with massive pulmonary embolism, echocardiography should be considered an ancillary rather than a principal diagnostic test for pulmonary embolism.[4,6] Similar features of right ventricular dysfunction could be seen in other condition also *i.e.* COPD, cardiomyopathy.

Arterial blood gases

The characteristic changes are a reduced PaO_2, and an arterial carbon dioxide pressure ($PaCO_2$) that is normal or reduced because of hyperventilation. The PaO_2 is almost never normal in the patients with massive pulmonary embolism but can be normal in minor pulmonary embolism, mainly due to hyperventilation. In such cases the widening of the alveolo-arterial PO_2 gradient (> 20 mm Hg) may be more sensitive than PaO_2 alone.[7]

Lung scintigraphy

The lung scan is an indirect method of diagnosis since it does not detect the embolus itself but only its consequence, the perfusion abnormality. Pulmonary embolism usually produces a defect of perfusion but not ventilation ("mismatch") while most of the other conditions produce a ventilation defect in the same area as the perfusion defect (matched defects). The probability that perfusion defects are due to pulmonary embolism can be assessed as high, intermediate, or low depending on the type of scan abnormality.[8]

A normal perfusion scan essentially excludes the diagnosis of a recent pulmonary embolism because occlusive pulmonary embolism of all types produces a defect of perfusion. It may be useful as a first line imaging investigation only in patients with a normal chest radiograph and with no concurrent cardiopulmonary disease.[8]

Spiral computed tomography

Computed tomography pulmonary angiography, (CTPA) has emerged as a valuable method for diagnosing pulmonary embolism and because of its availability; it is becoming the first choice method. The technique is faster, less complex, and less operator dependent than conventional pulmonary angiography, and has about the same frequency of technically insufficient examinations (about 5%). The thorax can be scanned during a single breath hold. There is better interobserver agreement in the interpretation of CTPA than for scintigraphy. Another advantage of CTPA over scintigraphy is that by imaging the lung parenchyma and great vessels, an alternative diagnosis (for example, pulmonary mass, pneumonia, emphysema, pleural effusion, mediastinal adenopathy) can be made if pulmonary embolism is absent.[9] This advantage of CTPA also pertains to conventional pulmonary angiography, which images only the arteries. Computed tomography can also detect right ventricular dilatation, thus indicating severe, potentially fatal pulmonary embolism.[9]

Magnetic resonance imaging (MRI)

MRI offers both morphological and functional information on lung perfusion and right heart function, but its image quality still needs improvement to be comparable with computed tomography. Attractive advantage is the avoidance

of nephrotoxic iodinated contrast and ionizing radiation. This technique may ultimately allow simultaneous and accurate detection of both DVT and pulmonary embolism.[10] A disadvantage of MRI compared with computed tomography is the long time needed to perform the examination, which is not suitable for clinically unstable patients.[10]

Approach to the Patient with Suspected Pulmonary Embolism

All patients with possible PE should have clinical probability assessed and documented. The pre-test clinical probability score is an assessment of the clinical likelihood of pulmonary embolism, based on numerous clinical and risk factor markers. Clinical assessment has been shown to be useful for reducing the requirement for invasive tests in outcome studies[11] and to be cost-effective.[12] There are several clinical models to predict pre-test probability of pulmonary embolism e.g. Wells prediction rule, Geneva score and revised Geneva score. The most commonly used is Wells prediction rule (Table 1).

Table 1 Wells Prediction Rule for Predicting Pretest probability of Pulmonary Embolism[13]

Clinical Characteristic	Score
Previous PE or DVT	+1.5
Heart rate > 100 beats per minute	+1.5
Recent surgery or immobilization	+1.5
Clinical signs of DVT	+3
Alternative diagnosis less likely than PE	+3
Hemoptysis	+1
Cancer	+1

Note: Clinical probability of pulmonary embolism:

0-1	low
2-6	intermediate
> 7	High

Dimer assay

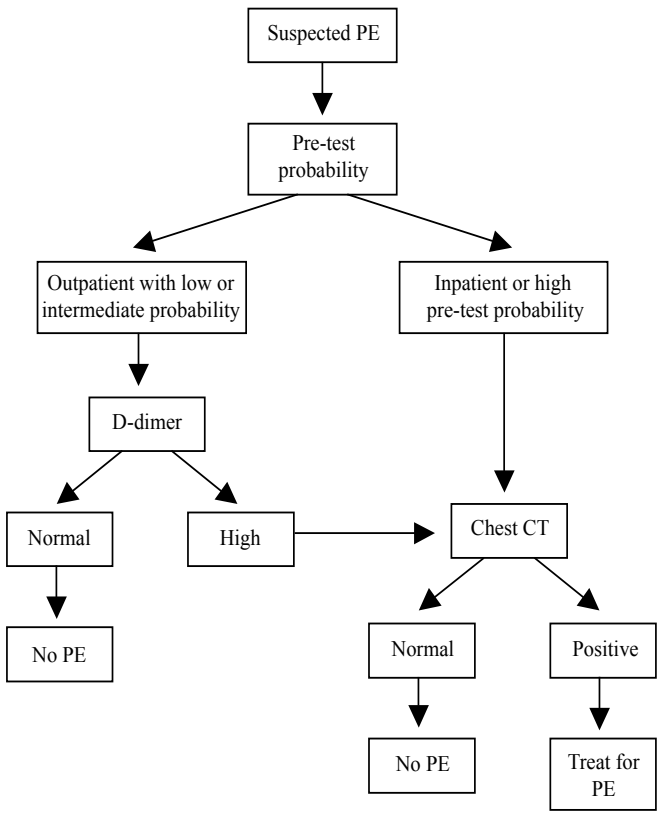
A nonspecific marker of fibrinolysis, D-dimer, as measured by ELISA, offers a high sensitivity and high negative predictive value and therefore has utility in the exclusion of PE, especially in the emergency room setting.[14] The D-dimer ELISA can be used to exclude PE in outpatients with a low to moderate suspicion without the need for further costly testing.[14]

The following flow chart depicts a simplified approach to the diagnosis of PE in emergency department.[14]

Risk Stratification (Fig. 1)

Patients with pulmonary embolism (PE) present with a wide spectrum of clinical acuity that necessitates different therapeutic strategies.

Figure 1



Most patients with PE present with normal blood pressure. However, some may rapidly deteriorate and manifest systemic hypotension, cardiogenic shock, and sudden death despite therapeutic levels of anticoagulation. Risk stratification to identify such patients has emerged as a critical component of care.[15]

Echocardiography

Echocardiography is considered the gold standard for the assessment of right ventricle dysfunction

in patients with pulmonary embolism.[16] From a prognostic point of view, echocardiography helps to classify patients with PE into 3 groups: [17]

RV Dysfunction	Hypotension	Hospital mortality
No	No	< 4%
Yes	No	5-10%
Yes	Yes	> 30%

Some evidence now supports the use of thrombolysis for hemodynamically stable, submassive pulmonary embolism, in association with pulmonary hypertension or right ventricular dysfunction.[18] The major drawbacks of echocardiography are its limited round-the-clock availability, its cost and is occasional poor imaging quality of the right ventricle, particularly in patients with obesity or chronic lung disease

Cardiac biomarkers

Cardiac biomarkers, including troponins and natriuretic peptides, have emerged as promising tools for risk assessment of patients with acute PE. Elevations of troponin levels in PE patients are mild and of short duration compared with elevations in patients with acute coronary syndromes.[19] Both cardiac troponins, and NT proBNP are associated with right ventricular dysfunction in acute PE and they correlate well with the extent of right ventricular dysfunction.[20]

In a recent study of patients of PE who were normotensive at presentation, correlation of cardiac biomarkers with mortality was as follows: [21]

NT proBNP	Troponin T	40 days Mortality
< 600 ng/L	< 0.07 mg/L	Nil
> 600 ng/L	< 0.07 mg/L	11%
> 600 ng/L	> 0.07 mg/L	33%

A latest meta analysis of 20 trials involving 1985 patients also confirmed that elevated troponin T and I are associated with high short term mortality. These data suggest that even normotensive patients should be carefully evaluated further for possibility of thrombolysis if biomarkers are positive.[20]

Thrombolytic Therapy

Thrombolysis has several theoretical advantages over simple anticoagulation with heparin. It should promote faster clot lysis and more rapid improvements in pulmonary perfusion and hemodynamic imbalances; it would also reduce chronic vascular obstruction and the potential for pulmonary hypertension. Thrombolysis would also eliminate venous thrombi, and hence reduce the incidence of recurrent emboli.[22] But despite its theoretical advantages thrombolysis still remains controversial due in part to the inadequate evidence demonstrating an improvement in outcome. Current BTS guidelines suggest its use only in massive PE. The BTS guidelines for thrombolysis only for circulatory compromise are based on a very small study of 8 patients with shock related to massive PE. The four patients receiving heparin died, whereas the four receiving thrombolysis survived.[23]

On unselected patients with PE, the evidence for thrombolysis is even less robust. There are very few randomized controlled trials of PE thrombolysis vs. heparin, with a combined total of < 800 patients.[24] No significant improvement in mortality or the incidence of recurrent PEs could be demonstrated in any of these studies.[24, 25]

Right ventricular dysfunction is generally accepted as a predictor of mortality in hemodynamically stable PE. This subgroup has started to be investigated with regard to the potential benefits of thrombolysis. A recent randomized study of thrombolysis in 256 patients with preserved systemic blood pressure but right ventricular dysfunction, showed that thrombolysis in these patients led to a reduction in the combined end point of mortality and need for escalation of therapy. But, no significant change in mortality alone was noted.[18]

On the basis of these studies, some authors have suggested that patients should be risk-stratified with echocardiography, and thrombolysis used for normotensive patients with pulmonary embolism who have moderate or severe right ventricular dysfunction.[26] Studies are also investigating whether

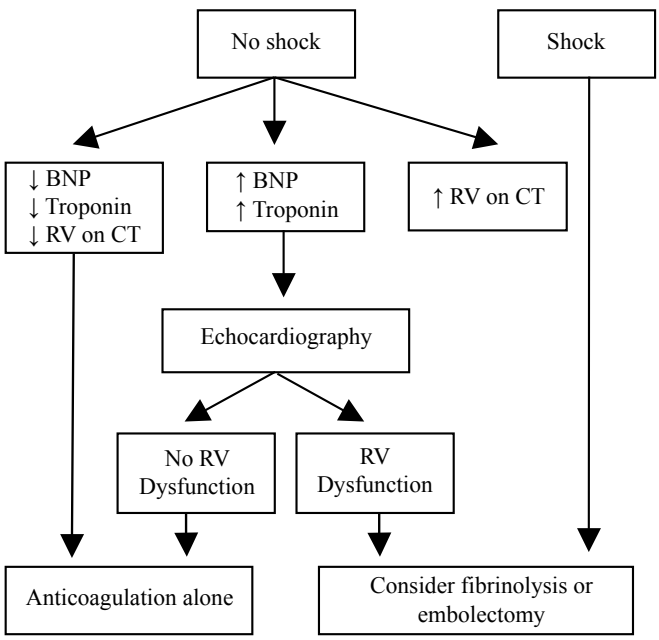
some of the cardiac biomarkers (troponin and brain natriuretic peptide) may be used as surrogates of right ventricular dysfunction and used in such a stratification of risk.[17]

Current ACCP guidelines for use of thrombolytics in Acute PE are as follows[27]

- For most patients with PE, systemic thrombolytic therapy is not recommend.
- For patients who are hemodynamically unstable, ACCP suggest use of thrombolytic therapy.
- Local administration of thrombolytic therapy via a catheter is not recommend.
- Thrombolytic regimens with a short infusion time are preferred over those with prolonged infusion times.

streptokinase	250000-IU loading dose followed by 100000 IU/h for 24 h.
Urokinase	4400 IU/kg body weight loading dose followed 2200 IU/kg for 12h
tPA	100-mg infusion over 2 h.
Reteplase	two separate IV boluses of 10 U approximately 30 min apart

Algorithm for PE management[15]



Tenecteplase has shown promising result in acute myocardial infarction. Although at present there is not enough evidence, it should also be as effective in pulmonary embolism.[28]

Heparin should not be infused concurrently with streptokinase or urokinase. For tPA or reteplase, concurrent use of heparin is optional.[27]

Role of unfractionated and low molecular weight heparin

UFH has been shown to be effective in the treatment of PE in comparison to no treatment.[27] Meta-analyses of studies in patients with DVT (with likely asymptomatic PE in a substantial proportion of these patients) have shown that LMWH treatment administered SC in doses adjusted to body weight only is at least as effective and safe for initial treatment as IV, dose-titrated UFH.[27]

Recommendations

1. For patients with objectively confirmed nonmassive PE, treatment with SC LMWH, or IV UFH for at least 5 days is recommended.
2. In patients with severe renal failure, IV UFH is preferred over LMWH.
3. If IV UFH is chosen, it should be administered by continuous infusion with dose adjustment to achieve and maintain an aPTT prolongation corresponding to plasma heparin levels from 0.3 to 0.7 IU/mL anti-Xa activity by the amidolytic assay.
4. We recommend initiation of Vitamin K antagonist together with LMWH or UFH on the first treatment day and discontinuation of heparin when the INR is stable and > 2.0.

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