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Review Article

Acute pulmonary embolism

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Abstract. Pulmonary embolism is a common illness with a potential for considerable morbidity and mortality. It is often misdiagnosed because patients present with a wide array of symptoms and signs. The clinical setting can raise suspicion, and certain inherited and acquired risk factors predispose susceptible individuals. A quantitative D-dimer level in the blood is the best screening test where pretest clinical probability is low. Computed tomographic angiography has become the most commonly used modality for diagnosis in all other settings. Treatment requires rapid and accurate risk stratification before development of right ventricular dysfunction and cardiogenic shock. Anticoagulation is the cornerstone of treatment. Thrombolysis is mainly indicated in patients with hemodynamic compromise and hypotension. Right ventricular dysfunction on echocardiography identifies another high-risk group who might require thrombolysis even if normotensive on presentation. This article reviews the current concepts in the diagnosis and management of pulmonary embolism.

Key words: Pulmonary embolism, pulmonary thromboembolism, venous thromboembolism, deep venous thrombosis

1. Introduction

Pulmonary embolism (PE) is a common and a potentially life threatening condition associated with considerable morbidity and mortality (1). In fact, an estimated 10 percent of symptomatic PE causes death within one hour of onset (2,3). The clinical presentation of PE is unfortunately variable and nonspecific, making an accurate diagnosis difficult. PE can be classified as acute or chronic. Patients with acute PE typically develop symptoms and signs immediately after obstruction of pulmonary vessels whereas patients with chronic PE present with symptoms over months to years due to pulmonary hypertension. In this article, we review the literature on the epidemiology, pathophysiology, clinical presentation, diagnosis and management of acute PE. Though PE refers to obstruction of the pulmonary artery or any of its branches by any material (e.g., thrombus, tumor, air, or fat) that originated elsewhere in the body, this review focuses on PE due to thrombus since it occurs secondary to venous thromboembolism (VTE) in most instances.

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2. Definitions

Acute PE can be further classified as massive, submassive and non-massive (1). *Massive PE* is characterized by the presence of hemodynamic instability (traditionally defined by the presence of systolic blood pressure less than 90 mm Hg). Patients with massive acute PE fall in the most critical group that requires immediate reperfusion therapy. *Submassive PE* is defined by the presence of right ventricular dysfunction but without hemodynamic instability. This entity is primarily diagnosed on echocardiography, and patients with submassive PE are currently considered to be at higher risk of morbidity and mortality than those without right ventricular dysfunction. All acute PE not meeting the definition of massive or submassive PE are considered *non-massive PE*. A *saddle PE* is a PE that lodges at the bifurcation of the main pulmonary artery into the right and left pulmonary arteries (4). Most saddle PEs are submassive. The presence of a mobile clot in the right heart is known as *right heart thromboemboli* (RHTE) or thrombus-in-transit and is also claimed to distinguish a particularly severe form of PE (5).

3. Epidemiology

The exact incidence of PE remains unknown because the diagnosis is not suspected in the vast majority. In a study of more than 42 million deaths that occurred over a 20-year duration, almost 600,000 patients (approximately 1.5 percent) were diagnosed with PE, and was the presumed cause of death in approximately 200,000 (6). This study certainly underestimates the true incidence and prevalence of PE, since more than half of all PE are undiagnosed (7). An estimated 100 persons per 100,000 each year develop venous thromboembolism for the first time, and the incidence rises exponentially from less than five cases per 100,000 persons in the second decade to approximately 500 cases (0.5 percent) per 100,000 persons at the eighth decade (2). The exact incidence of PE in India remains unknown (8). In a post-mortem study of 1000 autopsies from India, the overall incidence of PE in adult medical autopsies was 15.9 percent and was a terminal event in almost 80 percent of these patients (9).

4. Natural history of pulmonary embolism

The clinical syndromes of PE and deep venous thrombosis (DVT) are now considered part of a spectrum of dysregulated hemostasis within the venous system designated as venous thromboembolism (VTE) (10,11). Most DVTs start in the calf (12,13). About half of such calf DVTs resolves spontaneously within 72 hours, and only about one sixth extend to involve the proximal veins (13,14). Thrombi that remain confined to the calf rarely if ever cause symptomatic PE (12,13,15). The risk that a calf DVT will extend proximally and subsequently cause PE increases with the severity of the initiating prothrombotic stimulus and the initial size of the thrombus (13,14,16). Although acute VTE usually presents with either leg or pulmonary symptoms or both, most patients have thrombosis at both sites at the time of diagnosis. Approximately one-third of patients with symptomatic VTE manifests as PE whereas two-thirds manifest DVT alone (2). Forty to 50 percent of patients with symptomatic proximal DVT without symptoms of PE have ventilation-perfusion lung scan findings associated with a high probability of embolism (17-21). Since the sensitivity of a high-probability lung scan for PE is only 50 percent, it is probable that PE occurs with most episodes of symptomatic proximal DVT (22,23). Proximal DVTs resolve slowly during treatment with anticoagulants, and thrombi remain detectable in half of the patients after a year (3,24-28). Resolution of DVT is less likely in patients with a large initial thrombus or cancer (27). Ten percent of patients with symptomatic DVTs develop severe post-thrombotic syndrome within five years, and recurrent ipsilateral DVT increases this risk (29,30).

About 10 percent of PEs are rapidly fatal (31,32). Mortality rates after an episode of PE are fairly high with 25 percent of patients dying within one year (33-39). Five to 10 percent of patients with PE present with shock that is associated with a mortality rate of almost 25 to 50 percent (36,40-42). About 50 to 70 percent of patients with symptomatic PE have DVT, and involve the proximal veins in about two thirds of cases (43). However, only about 25 percent of patients with symptomatic PE have clinical evidence of DVT (44) whereas DVT is demonstrated on compression ultrasonographic examination in about 40 to 50 percent (45). About 50 percent of diagnosed PE is associated with right ventricular dysfunction, which is associated with five-fold greater in-hospital mortality (34,36,42,46). There is 50 percent resolution of PE after a month of treatment, and perfusion eventually returns to normal in two-thirds of patients (46-52). About 5 percent of treated patients with PE develop pulmonary hypertension because of poor resolution of the thromboemboli (38).

Approximately 20 to 50 percent episodes of first-time VTE are unprovoked that occur without a readily identifiable risk factor (2). Early mortality after VTE is strongly associated with presentation as PE, advanced age, cancer, and underlying cardiovascular disease (53-54). Despite anticoagulant therapy, VTE recurs frequently in the first few months after the initial event, with a recurrence rate of seven percent at six months (2,3,7,53-56). Death occurs in six percent of DVT and 12 percent of PE cases within a month of diagnosis (2,3,7,29,36,53-59). After a course of treatment, the risk of recurrent thrombosis is higher in patients without reversible risk factors, in those with cancer, and in those with prothrombotic biochemical abnormalities such as antiphospholipid antibodies and homozygous factor V Leiden (2,3,7,53,54).

5. Risk factors

VTE is currently regarded as the result of the interaction between patient-related (usually irreversible) and setting-related (usually reversible) risk factors. There are three factors that can contribute to the development of venous thrombosis, and include hypercoagulability, stasis and endothelial injury. Although PE can occur

without any predisposing cause, one or more causes can usually be identified. Venous stasis from any cause such as major surgery, is a major predisposing factor for VTE (10). All cancers increase risk, although adenocarcinoma is the most recognized malignancy associated with VTE. Other acquired conditions that predispose patients to VTE include elevated levels of antiphospholipid antibodies, hyperhomocysteinemia, and certain chronic diseases such as polycythemia. Inherited hypercoagulable states or thrombophilias are the other common predisposing factors for unprovoked PE. The proportion of patients with idiopathic or unprovoked PE was about 20 percent in the International Cooperative Pulmonary Embolism Registry (ICOPER) (36). Thrombophilias can be broadly classified into two types - those associated with reduced levels of the inhibitors of the coagulation cascade (e.g. protein C, S and antithrombin deficiency) and thrombophilias associated with increased levels or function of the coagulation factors (e.g. Factor V Leiden) (60).

6. Pathophysiology

The consequences of acute PE are primarily hemodynamic and usually become apparent when at least 30 to 50 percent of the pulmonary arterial bed is occluded by thrombi (61). As pulmonary vascular resistance increases, right ventricular pressure rises and causes right ventricular dilatation with resultant bulge of the interventricular septum into the left ventricle. This results in reduced left ventricular distensibility and impaired filling during diastole. Increased right ventricular wall tension also compresses the right coronary artery, and may precipitate myocardial ischemia and infarction. Underfilling of the left ventricle may lead to a fall in left ventricular cardiac output and systemic arterial pressure, thereby provoking myocardial ischemia due to compromised coronary artery perfusion. Eventually, circulatory collapse and death may ensue (62).

Respiratory insufficiency in PE is predominantly a consequence of hemodynamic disturbances (62). The most common gas exchange abnormalities are hypoxemia and an increased alveolar-arterial oxygen tension gradient secondary to ventilation-perfusion mismatch (due to zones of reduced flow and zones of overflow of the capillary bed served by non-obstructed vessels). Low cardiac output results in the desaturation of mixed venous blood entering the pulmonary circulation. Release of mediators such as serotonin and others can produce ventilation-perfusion mismatching at sites remote from the embolus, thereby accounting for a potential discordance between a small PE and a large alveolar-arterial oxygen gradient. These mediators can also increase airway resistance due to constriction of airways distal to the bronchi. An increase in the physiologic dead space occurs as ventilation to gas exchange units exceeds venous blood flow through the pulmonary capillaries that also can contributes to hypoxemia. In about one-third of patients, right-to-left shunt through a patent foramen ovale induced by an inverted pressure gradient between the right and left atrium may lead to severe hypoxemia. Finally, decreased pulmonary compliance due to lung edema, lung hemorrhage, or loss of surfactant also contributes to hypoxemia (1).

7. Clinical presentation

In considering a possible diagnosis of acute PE, it is helpful to consider the patient in terms of the mode of presentation. The three major symptom complexes that occur in conjunction with PE are pulmonary infarction (pleuritic chest pain and/or hemoptysis), isolated dyspnea and circulatory collapse (63,64). The clinical presentation also has a bearing on outcome with a reported isolated dyspnea and circulatory collapse compared to 2.5 percent for pulmonary infarction (63). In any patient presenting with pleuritic chest pain and a pleural effusion, PE is a strong diagnostic possibility (65). In a study of 22 patients who presented to the emergency department with pleuritic chest pain and a pleural effusion, 12 (55 percent) had PE (66). mortality of 6.2 percent and 6.5 percent with

Dyspnea is a common accompaniment (82 percent in one series of 2,454 patients (67) of patients with PE and is out of proportion to the chest radiographic findings including the size of the pleural effusion. Almost 50 percent of the patients are febrile but temperature elevations above 38.5ºC and expectoration of purulent sputum occurs in less than 10 percent (44,68). Twenty to 45 percent of patients may complain of cough (44,67,68). In fact, if a patient has no dyspnea, tachypnea or pleuritic chest pain, PE is unlikely and overall only three to seven percent of patients with PE are totally asymptomatic at presentation (44,67,68).

8. Diagnosis of pulmonary embolism

The diagnosis of PE and pleural effusion can be easily made provided it is suspected, and is in fact, the first step in making the diagnosis (Fig. 1).

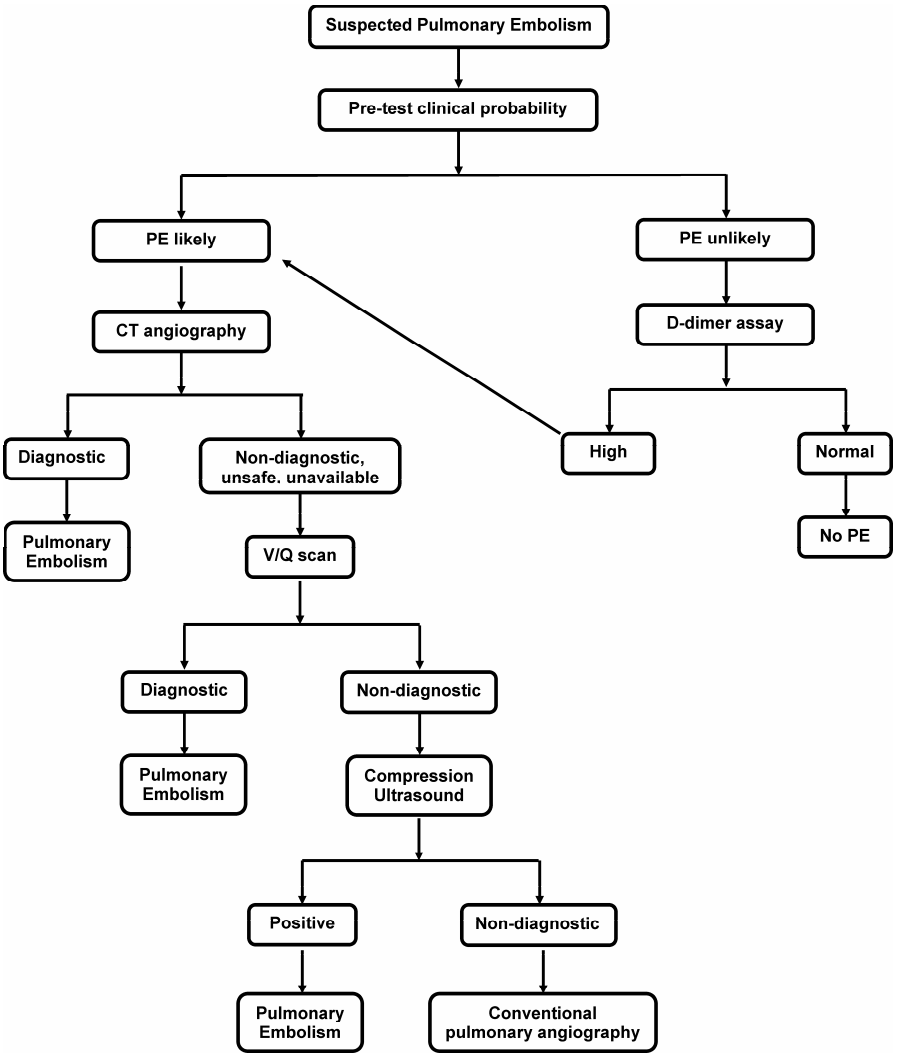

Fig. 1. Diagnostic algorithm for pulmonary embolism followed in our hospital

The Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study provided direct evidence that a pre-test clinical assessment allows for the stratification of patients into pretest categories of probability corresponding to an increasing prevalence of PE (23). Currently, a simplified clinical decision rule based on the modification of the Well's criteria is now widely used to risk stratify the patient in to two categories- PE likely and PE unlikely (Table 1) (69).

8.1.Pulmonary embolism unlikely after clinical assessment

In patients with a clinical decision rule score less than or equal to four, the next step is to order a quantitative D-dimer enzyme linked immunosorbent assay (ELISA). The D-dimer can be currently detected through five methods- quantitative ELISA, latex agglutination assay, immunofiltration assay, immunoturbidimetric assay and the simpliRED D-dimer assay.

Table 1. Simple clinical decision rule based on modified Well's criteria

Variable	Points
Clinical signs and symptoms of deep vein thrombosis	3
Alternative diagnosis less likely than pulmonary embolism	3
Heart rate > 100/min	1.5
Immobilization (>3 d) or surgery in the previous 4 weeks	1.5
Previous pulmonary embolism or deep vein thrombosis	1.5
Hemoptysis	1
Malignancy	1

"PE unlikely" ≤ 4 points; "PE likely" >4 points

In a meta-analysis, the sensitivities of the enzyme-linked immunofluorescence assay, microplate ELISA and latex quantitative assay were 97, 95 and 95 percent respectively, and were superior to those of the whole-blood D-dimer assay (87 percent), latex semiquantitative assay (88 percent) and latex qualitative assay (75 percent) (70). Thus, when the quantitative rapid ELISA is used in combination with an objective clinical assessment (PE unlikely), the post-test probability of PE ranges from 0.2 to 1.1 percent with a normal D-dimer result (69, 71). No further testing is generally required in this group of patients (72). In some centers, additional compression ultrasound of the lower limb is used in this group of patients but is optional (73).

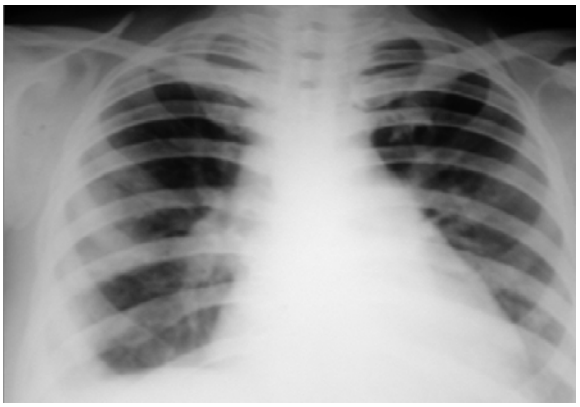

Fig. 2. Chest radiograph shows blunting of the right costophrenic angle with peripheral non-homogenous pulmonary opacities in the right mid zone

8.2.Pulmonary embolism likely after clinical assessment

In patients who have a high clinical probability for PE i.e. a score more than four (or a low clinical probability but a positive D-dimer assay), the investigation of choice is multi-detector computed tomographic angiography (CTA) of the chest. D-dimer is not recommended in this subset of patients as a negative D-dimer is associated with a 15 percent probability of PE (71). CTA has virtually replaced ventilation-perfusion (V/Q) scans as the investigation of choice in a patient with suspected PE. The initial studies were performed using single-detector CTA with a slice thickness of 3 to 5 millimeters and thus the sensitivities varied from 64 to 93 percent (Fig. 2). The shorter acquisition times, the thinner slice thickness with CTA will produce better images and would provide better evaluation of subsegmental emboli.

The PIOPED study (23) indicated that a high probability V/Q scan is sufficient evidence to treat for PE and that therapy can be safely withheld in patients with a normal or near normal scans. Unfortunately, only 16 percent of the patients with suspected PE had high probability scans and only 8 percent had normal or near normal scans. Nearly 44 percent had intermediate probability scans that neither confirmed nor excluded PE. The incidence of PE in patients with intermediate probability scans was 33 percent. Also, the inter-observer agreement is better for CT than for V/Q scanning (74). In

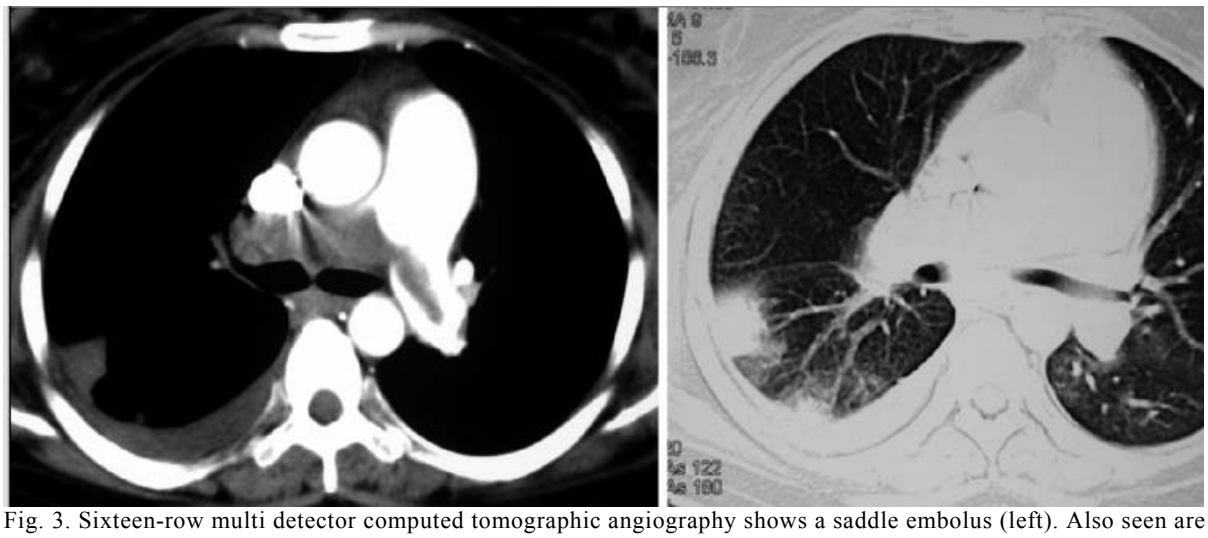

Fig. 3. Sixteen-row multi detector computed tomographic angiography shows a saddle embolus (left). Also seen are right pleural effusion and peripheral pulmonary opacities. The pulmonary opacities are better appreciated in the lung windows (right).

patients with pleural effusion, V/Q scan is not further indicated as it leads to a non-diagnostic scan.

In the recently conducted PIOPED II study, the specificity of CTA chest was 96 percent and the sensitivity was 83 percent (75). This is higher than that of single-detector imaging, which is approximately 70 percent (76,77) and exceeds that of high probability lung scans (sensitivity and specificity; 41 and 97 percent respectively) (23). Thus if the test is positive then one would go ahead with treating the patient but if the test is negative in a patient with high clinical probability then further tests would be required to exclude PE. These include computed tomographic venography (negative predictive value 82 percent in patients with clinical high pretest probability (75), compression ultrasound of the lower limbs (positive predictive value of 75 percent in patients asymptomatic for DVT (78) and digital subtraction angiography (gold standard for diagnosis of PE). This is because the negative predictive value of CTA chest in a patient with high clinical probability is only 60 percent compared to a negative predictive value of 93 percent with low clinical probability (75).

It is important to remember that V/Q scans are characterized by matched V/Q defects corresponding to radiographically evident pleural effusions or other chest radiographic abnormalities and may be interpreted as low to intermediate probability for PE, and thus may not be reliable for the diagnosis of PE in the presence of a pleural effusion (79,80). In patients with chronic obstructive pulmonary disease (COPD) and suspected PE, V/Q scans are not recommended as multiple perfusion and ventilation abnormalities are frequently observed in COPD lungs even in the absence of VTE (81). In all such situations especially those with pre-existing pulmonary disease, CTA is the investigation of choice.

Importantly, in highly unstable patients such as those with hypotension or shock, the diagnosis of PE may be accepted on the basis of compatible indirect echocardiographic findings alone (1). If the patient is stabilized by supportive treatment, a definite diagnosis should be sought, and in these situations CT is very likely to confirm the diagnosis because of the high thrombus load in the pulmonary circulation. Conventional pulmonary angiography should be generally avoided as because it carries a risk of mortality in unstable patients (82).

Other investigations: Most patients undergo a chest radiograph, electrocardiogram and arterial blood gas analysis. These tests cannot be relied on to either confirm or rule out PE, because of their nonspecific nature. However, these tests help in further strengthening the clinical suspicion and are recommended in majority of the admitted patients (44, 64, 68, 83).

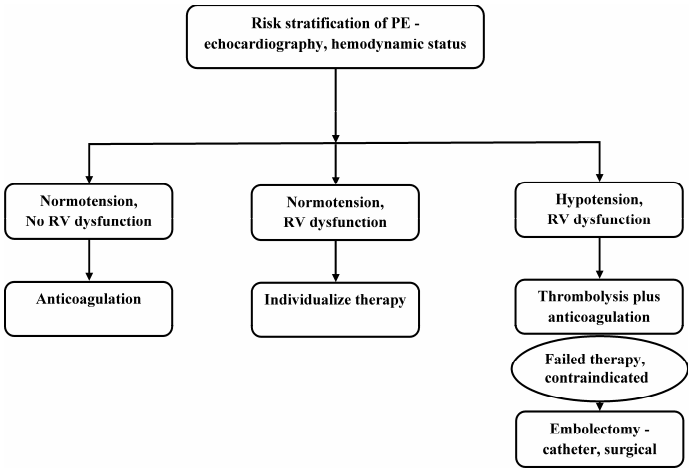

Fig. 4. Algorithm for management of pulmonary embolism

9. Treatment of pulmonary embolism

Hemodynamic and respiratory support is generally necessary in all patients with suspected or confirmed PE presenting with shock or hypotension. The treatment of PE can be divided into *primary therapy*, which consists of clot dissolution with thrombolysis or removal of PE by embolectomy or *secondary prevention* with anticoagulation or placement of an inferior vena caval (IVC) filter of recurrent PE rather than primary therapy. The primary therapy of PE is guided by the hemodynamic status of the patient and echocardiographic findings of right ventricular dysfunction (Fig. 4). In a patient who is suspected to have PE but is hemodynamically unstable, thrombolysis can also be initiated on indirect evidence on bedside echocardiography as the patient may be too sick to be shifted to a radiology suite.

Thrombolysis: There is no conclusive evidence till date to show that fibrinolysis reduces mortality in massive PE, except a small study which consisted only of eight patients (40). However, most authorities (84,85), tend to agree on this indication because thrombolytic therapy rapidly resolves thromboembolic obstruction and exerts beneficial effects on hemodynamic parameters (46, 52, 86-102). Hence, thrombolytic therapy is currently considered the first-line treatment in patients with high-risk PE presenting with cardiogenic shock and/or persistent arterial hypotension (Table 2). It is however prudent to perform echocardiography prior to thrombolysis

as absence of right ventricular dysfunction in a hypotensive patient suspected with PE represents some other etiology of hypotension.

Table 2. Dose of commonly used fibrinolytic agents

Agent	Dose
Streptokinase	1.5 million IU over two hours
Urokinase	3 million IU over two hours
Alteplase	100 milligrams over two hours

Routine use of thrombolysis in submassive PE is not recommended, but may be considered in selected patients after thorough consideration of conditions increasing the risk of bleeding (103). The Management Strategies and Prognosis of Pulmonary Embolism-3 Trial (MAPPET-3) demonstrated a reduction in the need for escalation of therapy among patients receiving alteplase but the use of alteplase was not associated with increased survival (104). Currently, we thrombolyse patients of submassive PE only if they are demonstrated to have right ventricular dysfunction on echocardiography and hypoxemia (PaO_2 less than 60 mm Hg) (8).

The role of thrombolysis in patients who have RHTE is also controversial. Current evidence does not suggest the routine use of thrombolysis in patients with RHTE. It is the clinical presentation rather than the presence of RHTE that should dictate management decisions (5).

Thrombolytic therapy is currently not indicated in non-massive PE. Thrombolysis carries a significant risk of bleeding (up to 13 percent cumulative rate of major bleeding and up to two percent risk of intracranial/fatal hemorrhage) especially when predisposing conditions or comorbidities exist (1). In the most recent of these trials, life-threatening hemorrhage has been less common, in line with the observation that thrombolysis related bleeding rates are lower when non-invasive imaging methods are used to confirm PE (105).

Anticoagulation: Anticoagulation is a critical component in the management of all patients with PE, and should be started immediately pending investigations. The need for immediate anticoagulation in patients with PE is based on a landmark study performed in 1960, which demonstrated the benefits of unfractionated heparin (UFH) in comparison with no treatment (106). Treatment is initiated with heparin 80 units per kilogram as a bolus injection followed by infusion of 18 units per kilogram per hour titrated according to activated partial thromboplastin time (Table 3) and is followed by three to six months of oral anticoagulation with warfarin to maintain an international normalized ratio between two and three.

Table 3. Titrating dose of unfractionated heparin based on activated partial thromboplastin time

Activated partial thromboplastin time	Change of dosage
Less than 35 seconds (less than 1.2 times control)	80 U/kg bolus); increase infusion rate by 4 U/kg/hour
35 to 45 seconds (1.2 to 1.5 times control)	40U/kg bolus; increase infusion rate by 2 U/kg/hour
46 to 70 seconds (1.5 to 2.3 times control)	No change
71 to 90 seconds (2.3 to 3.0 times control)	Reduce infusion rate by 2 U/kg/h
More than 90 seconds (more than 3.0 times control)	Stop infusion for one hour; then reduce infusion rate by 3U/kg/h

Low-molecular weight heparin (LMWH) is equivalent in efficacy to UFH in the treatment of PE, and in selected patients can be even used in the outpatient setting (107). The advantages of LMWH over UFH include a longer half-life, increased bioavailability, and a predictable dose response (Table 4). Moreover, LMWHs are administered subcutaneously and usually do not require dose adjustments or laboratory monitoring (108).

In patients with massive PE, UFH is the recommended therapy because of unpredictable absorption of subcutaneous injections of LMWH.

Table 4. Dose of commonly used low-molecular weight heparins

Agent	Dose	Frequency
Enoxaparin	1 mg/kg	twice daily
Dalteparin	120 IU/kg	twice daily
Fondaparinux	5 mg (weight less than 50 kg)	once daily
	7.5 mg (weight 50 to 100 kg)	
	10 mg (weight more than 100 kg)	

In a recent trial in which UFH was administered subcutaneously as an initial dose of 333 units per kilogram followed by a fixed dose of 250 units per kilogram every 12 hours not only found UFH as effective and safe as LMWH in patients with acute VTE but also suitable for outpatient treatment (109). The presence of hemorrhagic fluid is not a contraindication to anticoagulation (or thrombolysis), and in fact, with treatment the pleural effusions gradually resolve. If a patient develops increasing pleural effusion, dyspnea, recurrent chest pain or a contralateral effusion, recurrent PE should be excluded.

10. Other approaches

Surgical pulmonary embolectomy is a valuable therapeutic option in patients with high-risk PE in whom thrombolysis is absolutely contraindicated or has failed (110). Catheter embolectomy or fragmentation of proximal pulmonary arterial clots may be considered as an alternative to surgical treatment in high-risk PE patients when thrombolysis is absolutely contraindicated or has failed (111). Catheter techniques should only be used in the main arteries since fragmentation within the smaller branches is unlikely to be of benefit and may damage the more delicate structures, with risk of perforation (112). The systematic use of permanent vena cava filters in the general population with VTE is not recommended. In the only randomized controlled trial, 400 patients received either IVC filters with concomitant anticoagulation or anticoagulation alone. Even though the total number of VTE events was similar in both groups (36.4 vs.35.4 percent; filter versus no filter respectively), those with an IVC filter experienced a greater cumulative incidence of symptomatic DVT (35.7 vs. 27.5 percent), but significantly fewer symptomatic PE (6.2 vs. 15.1 percent) (113,114). The incidence of post-thrombotic syndrome was not different between groups. Currently, retrievable IVC filters are indicated in patients where anticoagulants cannot be used or those in whom anticoagulation has failed to prevent recurrent VTE (115).

11. Conclusions

The diagnostic workup for patients with suspected PE should begin with an assessment of the clinical probability. When the probability of PE is unlikely, a negative d-dimer test by quantitative ELISA essentially rules out the diagnosis, whereas a positive result indicates the need for further testing, preferably multidetector CT scanning. In patients where the probability of PE is likely, MDCTA with compression ultrasound of lower limb veins is the investigation of choice. Anticoagulation therapy should be initiated promptly. The presence of hypotension defines a high-risk patient who requires aggressive management with thrombolytic therapy. The detection of right ventricular dilatation on echocardiography indicates the presence of an intermediate-risk PE. Thrombolytic therapy should be considered, but its role in such cases remains uncertain.

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