

Pulmonary Embolism Treatment: Current Developments and Approaches

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Abstract

Pulmonary embolism (PE) remains an important preventable condition with high mortality and morbidity, recurrence, and sometimes difficult diagnosis. Current treatments have evolved considerably and changed remarkably recently. PE is a condition requiring critical care, and rapid advances in this field have led to significant evolution in treatment strategies. The broad spectrum and severity of PE require individualization and optimization of treatment approaches. In addition to algorithms guiding the diagnostic process of patients, the use of risk classifications guiding the recognition of critically ill patients and the decision of treatment modalities has an important place in emergency department practice. This review addresses the latest developments for treating PE based on the current findings of epidemiological studies. Considering the characteristics of patient populations, clinical conditions, and comorbidities, a range of treatment options from anticoagulation therapies to catheter-based interventions, thrombolytic therapies, and alternative approaches will be examined. Changes in current guidelines affecting treatment decisions and the role of a multidisciplinary approach will also be emphasized. This review aims to synthesize the current knowledge in the field of PE treatment and will allow us to collectively interpret the most effective and safe treatment strategies for this critical condition.

Keywords: Pulmonary embolism, angioagulant therapy, systemic thrombolysis, catheter-related embolectomy

Introduction

Pulmonary embolism (PE) is a critical vascular condition affecting the pulmonary arterial system resulting from an embolism caused by venous thrombosis. Emboli resulting from the unfavorable course of deep vein thrombosis cause occlusions in the pulmonary arteries, leading to a serious condition that restricts lung perfusion. Clinical symptoms can vary over a wide spectrum and can cause potentially life-threatening complications that require timely diagnosis and intervention.

This review aims to provide a deeper understanding of PE cases and examine treatment strategies. Considering recent medical advances, available treatment options, and current literature will be reviewed, thus providing a basis for understanding the role of this important vascular event in the medical field.

When cases with suspected PE in the emergency department are analyzed, PE is the final diagnosis in approximately 35% of cases

with advanced imaging and investigations, and the prevailing mortality rate of 10% shows the complexity related to PE management. In recent years, increasingly effective treatment modalities, the use of advanced diagnostic tools, and increased adherence to guidelines have led to favorable developments in PE prognosis [1,2]. However, the use of diagnostic tests has increased nowadays because of the involvement of small branches or the diagnosis of PE without clinical significance. Although this has increased the incidence of PE cases, the same efficacy has not been demonstrated in terms of mortality and treatment complications.

This situation is a paradox in clinical practice. Diagnostic difficulties may lead to unnecessary treatment, whereas missed cases of PE may lead to potentially fatal outcomes. These challenges highlight the need for an important balancing act that influences clinical practice and guides treatment strategies.



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In PE diagnosis, the interpretation of symptoms and association with PE and clinical suspicion play an important role, and the algorithm followed by the clinical combination of risk factors may lead to a diagnosis [3]. Modified Geneva and Wells scoring systems are the most commonly used systems in clinical decision-making and risk determination [4,5]. While scoring systems allow the determination of the risk of PE in the patient, they may also guide the planning of the diagnostic stages. In these scoring systems, the PE expectancy in the low, medium, and high-probability groups is 10%, 30%, and 65%, respectively [6,7].

In patients with new-onset chest pain or shortness of breath presenting to the emergency department, considering PE without risk analysis increases the risk of misuse of excessive laboratory tests and imaging modalities in the differential diagnosis. PE exclusion criteria have been developed with a sensitivity of 97% for excluding the diagnosis, especially in patients with a low probability of PE. In the PROPER study, the correct and effective use of exclusion criteria in patient evaluation may reduce the use of computed tomography pulmonary angiography and may also reduce unnecessary follow-up periods when the waiting time of patients for laboratory and imaging results is considered [8,9].

In the diagnostic process, it is important to question provoking factors such as the patient's history of previous operations, trauma, bed rest and immobilization, pregnancy status, or use of hormone replacement therapy. These factors play a critical role in assessing the risk of possible thrombosis. However, there are cases of thrombosis occurring without any known provocative factor, which is an important factor in determining the course of treatment. Clinical evaluation of patients, history taking, and determination of risk factors help to accurately classify both provoked PE states and thrombosis developing without provocation and to develop a treatment plan [10].

Clinical symptoms are usually nonspecific, and the most common complaint is chest pain. Chest pain manifests as sudden onset pleuritic-type pain, particularly in distal pulmonary artery (PA) emboli, whereas it causes pressure and pain in the chest in the presence of large areas of centrally located thrombus [11]. In this case, in addition to PE, life-threatening causes of chest pain, especially acute coronary syndromes and acute aortic pathologies, should be considered.

Dyspnoea is a common symptom following chest pain in patients with PE. In particular, in individuals with previous cardiopulmonary disease, a sudden increase in dyspnoea and impaired oxygenation should suggest PE. Arterial blood gas examination is not always diagnostic, and normal values may be encountered in 40% of cases. However, hypoxia and hypocapnia and consequent respiratory alkalosis are the most common blood gas symptoms resulting from ventilation-

perfusion imbalance. Although chest radiography is far from diagnostic, it should be used to rule out other causes. Obtaining indirect findings may support the diagnosis [12,13].

Electrocardiographic (ECG) findings may also be helpful in the diagnosis of PE. The most common finding is sinus tachycardia. T wave changes between V1 and V4 may be seen as a reflection of right ventricular (RV) enlargement on ECG because of RV involvement. The S1Q3T3 pattern is unlikely to be seen and is not diagnostic alone. These findings are important guidelines in the ECG evaluation of PE and provide important clues for emergency management [14].

Hypotension and shock are important symptoms that indicate a high risk of the development of PE. However, most PE cases are in the intermediate- and low-risk groups. Clinical parameters such as low systolic blood pressure, tachycardia, tachypnea, and syncope adversely affect the short-term prognosis of PE.

Detection of myocardial damage because of RV involvement or acute pressure overload, particularly in patients in the medium-low risk class, is critical for determining a rapid and accurate prognosis. These clinical parameters play a vital role in determining treatment strategies [15-17].

In conclusion, in patients diagnosed with PE, an accurate assessment of both the basic findings indicating high-risk conditions and the prognosis in intermediate-low-risk groups is vital in establishing an effective and personalized treatment plan.

Treatment in the Acute Phase

Respiratory Support and Haemodynamic Stabilization

Hypoxaemia is an important sign of severe PE and is usually caused by a mismatch between ventilation and perfusion. Supplemental oxygen administration is necessary for patients with PE and arterial oxygen saturation <90%, which is considered a fundamental strategy in the management of acute respiratory failure due to hypoxaemia [18].

Hypoxaemia that develops because of ventilation and perfusion incompatibility may lead to severe respiratory failure that may become resistant to conventional oxygen support. Alternatively, high-flow oxygen or non-invasive mechanical ventilation techniques should be considered to be correct hypoxaemia [18-20]. Invasive mechanical ventilation may decrease venous return due to the positive intrathoracic pressure it creates. It may further deepen the existing hypotension with RV failure that develops especially in unstable patients due to severe PE. Therefore, this situation should be considered in the presence of an indication for invasive mechanical ventilation, and undesirable haemodynamic effects should be reduced with low tidal volume (6 mL/kg) and end-inspiratory plateau pressure (below 30 mmHg) [18,21].

Pharmacological Treatment for New-onset RV Failure

The most common cause of mortality observed in PE is impaired pump function and decreased volume due to RV involvement. Initiation of appropriate fluid therapy in these patients requires careful monitoring. Although delay in fluid replacement does not contribute to treatment, excessive fluid administration may deepen the dysfunction of the RV. Giving fluid replacement in a controlled manner according to the patient's current volume load and deciding the volume and rate of fluid replacement under the guidance of central venous pressure measurement or inferior vena cava imaging with ultrasonography represent a more accurate and effective approach [22,23].

Vasopressors, such as norepinephrine, increase myocardial perfusion and contractility without affecting peripheral vascular resistance and should be used especially in shock states. In patients with a low ejection fraction and normal blood pressure, dobutamine may be preferred. Vasodilators, such as inhaled nitric oxide has been reported to improve ventilation and perfusion by providing selective pulmonary vasodilatation and to be beneficial; however, extensive additional studies are needed [24].

Advanced Life Support

In the presence of pulseless electrical activity in cardiac arrest developing with non-shockable rhythm, acute PE should be considered as a cause of arrest. Advanced cardiac life support steps should be applied in cases of cardiac arrest due to PE. Thrombolytic treatment should be kept in mind, and resuscitation procedures should be continued for 60-90 minutes if a thrombolytic drug is administered [25,26].

Maintenance of cardiopulmonary resuscitation and circulation with mostly venoarterial extracorporeal membrane oxygenation (VA-ECMO) may be beneficial in high-risk PE patients, and successful case series have been reported in patients with circulatory collapse or cardiac arrest [27].

Initial Anticoagulation

Patients with high and moderate suspicion of PE should receive anticoagulant therapy while the diagnostic testing process is being performed. The anticoagulant agent of choice is often subcutaneous low molecular weight heparin (LMWH), fondaparinux, or intravenous unfractionated heparin (UFH) [28,29]. The decision should be based on the clinical condition of the patient and drug interactions. LMWH and fondaparinux may be preferred over UFH for initial treatment because they have a lower risk of major bleeding and heparin-induced thrombocytopenia.

Non-vitamin K antagonist oral anticoagulants (NOACs) are now the agents of choice for treating most patients with PE, both in the acute phase (with or without a short initial period of parenteral heparin or fondaparinux) and in the

longer term. Regardless of whether parenteral heparin is used in the first few hours or days after acute PE, the 2019 guidelines now recommend that a NOAC is preferred over a vitamin K antagonist when the decision is made to start oral anticoagulation [30,31].

Reperfusion Therapies

Systemic Thrombolysis

The clinical probability of suspected acute high-risk PE is usually high, and the differential diagnosis includes other life-threatening conditions such as cardiac tamponade, acute coronary syndrome, aortic dissection, acute valvular dysfunction, and hypovolemia. If acute PE causes hemodynamic decompensation, immediate bedside transthoracic echocardiography will detect acute RV dysfunction. In a highly unstable patient, echocardiographic evidence of RV dysfunction is sufficient to initiate immediate reperfusion without further testing. In intubated patients, transesophageal echocardiography can provide direct visualization of thrombi in the PA and its main branches, particularly in patients with RV dysfunction.

The 2019 guidelines recommend the establishment of a multidisciplinary team for the acute phase management of high-risk and (in selected cases) intermediate-risk PE, depending on the available resources and expertise in each hospital [8]. Primary reperfusion therapy includes systemic thrombolytic therapy to prevent circulatory shock. Surgical pulmonary embolectomy (SPE) or percutaneous catheter-directed therapy are alternative reperfusion options in patients with contraindications for thrombolysis, if expertise in either of these methods and appropriate resources are available [31,32].

In addition, the PE thrombolysis study examined the efficacy of thrombolytic therapy in normotensive intermediate-risk cases of PE. This study found a significantly better response with thrombolytic agents than with anticoagulants in hemodynamic instability, but a high risk of serious major bleeding and intracranial hemorrhage after thrombolytic therapy in these patients. Therefore, thrombolytic therapy in these patients should be carefully evaluated and possible complications should be considered [33].

Tissue plasminogen activator (rtPA), streptokinase, and urokinase are commonly used as thrombolytic agents. The most commonly preferred thrombolytic agent is rtPA, which is widely used because of its short half-life and ease of administration compared with other agents. rtPA is usually administered as an infusion of 100 mg/2 h for treating PE. Recent studies on half the classical dose of rtPA (50 mg/2 h infusion and 10 mg bolus + 40 mg/2 h infusion) have shown that although the same therapeutic effect is achieved, a lower rate of complications is observed [34,35].

Catheter-mediated Embolectomy

Mechanical reperfusion is achieved by PA catheterization via the femoral route. This includes mechanical fragmentation with different types of catheters, thrombus aspiration, or, more commonly, mechanical or ultrasound-assisted fragmentation with a pharmacomechanical approach and low-dose thrombolysis [36].

Surgical Embolectomy

Surgical embolectomy in acute PE is usually performed with aortic cross-clamping and cardioplegic cardiopulmonary bypass without cardiac arrest and incision of the pulmonary arteries with removal or resorption of fresh clots. Recent reports have shown favorable surgical outcomes in high-risk PE patients with or without cardiac arrest and in selected cases of PE [37]. Pulmonary embolectomy is recommended for individuals with submassive or massive PE under specific conditions. These include cases where there are contraindications to thrombolysis, unsuccessful outcomes following thrombolysis or catheter-assisted embolectomy, or instances where the patient is in a state of shock with a high likelihood of succumbing to the condition before the effects of thrombolysis can manifest, especially within a few hours. This surgical intervention is suitable when there is access to the necessary surgical expertise and resources [38].

Using thrombolysis and catheter thromboembolectomy can swiftly restore hemodynamic stability. However, these treatments carry the potential risk of causing distal fragment embolization and hemorrhage.

In cases involving high-risk situations and cardiogenic shock, SPE is a viable option. This is particularly applicable to patients with massive PE who are unsuitable candidates for fibrinolysis or exhibit instability even after its administration. In addition, individuals with submassive PE, in whom thrombolysis is either contraindicated or proves ineffective, and those with right heart thrombi situated close to or straddling a patent foramen ovale are also considered suitable candidates for surgical intervention [39].

Upon deciding to proceed with pulmonary embolectomy, it is imperative to swiftly move the patient to the operating room. In situations involving massive pulmonary embolism, it is advisable to establish VA-ECMO support before transitioning to the operating room. This precautionary measure mitigates the challenges associated with sudden and potentially disorderly induction of anesthesia and initiation of cardiopulmonary bypass. For severely ill patients with PE, VA-ECMO can be employed to provide life-saving support. In fact, VA-ECMO is frequently employed as a crucial intervention before opting for surgical embolectomy [40,41].

VA-ECMO stands out as a rapid and reliable mechanical circulatory support device that effectively reduces RV volume overload. Its application is also endorsed as a viable treatment for PE patients experiencing refractory circulatory collapse or cardiac arrest. Notably, the reported overall survival rate for patients undergoing VA-ECMO for severe PE ranges from 38% to 67%. Current guidelines advocate VA-ECMO as a transitional support mechanism leading to definitive reperfusion therapy [40,42].

The Class IIb recommendation for VA-ECMO is derived from various case series because there is a dearth of case-control or cohort studies directly comparing VA-ECMO with alternative treatments. Despite the absence of robust evidence, the use of VA-ECMO has seen a rise over time and has demonstrated improved outcomes in high-risk PE, as indicated by national studies [43,44].

Treatment Strategies

Emergency Treatment of High-risk PE

In high-risk PE patients, the initial treatment is acute reperfusion therapy, and in most cases, systemic thrombolysis is the preferred treatment protocol. In patients with contraindications to thrombolysis, alternative reperfusion strategies such as SPE or catheter embolectomy-guided therapy may be considered, depending on the experience of the clinic and hospital conditions. However, for these methods to be applied, expertise in the relevant field and appropriate resources should be available. After hemodynamic stabilization and reperfusion therapy, oral or parenteral anticoagulant therapy should be initiated. In particular, NOACs apixaban or rivaroxaban may be preferred [10].

Emergency Treatment of Intermediate-risk PE

For most acute PE cases without hemodynamic compromise, parenteral or oral anticoagulation (without reperfusion techniques) is adequate. In normotensive patients, at least one PE-related indicator or comorbidity should be treated with hospitalization. In this group, in the presence of evidence of RV dysfunction on echocardiography or pulmonary angiography or a positive troponin test result, patients should be monitored during the first hours and days and followed for hemodynamic decompensation.

Management of Low-risk PE: Triage for Early Discharge and Home Treatment

In low-risk PE cases, discharge from the emergency department and outpatient anticoagulant therapy may be considered after evaluation of certain criteria. Outpatient follow-up may be considered if the risk of mortality and morbidity is found to be low in the PE risk assessment and if the patient is in the low-

risk group in terms of existing complications. In addition, the patient should not have comorbid conditions and additional provoking factors that may worsen PE, and the patient should have social support to follow anticoagulation therapy on an outpatient basis.

Considering the commonly used exclusion criteria, in studies interpreting the use and efficacy of Hestia pulmonary embolism severity index (PESI) or simplified PESI, it was found that the rate of recurrent venous thromboembolism cases within 3 months was 2.3% and the mortality rate was 0.6% in patients discharged within 1 day and followed up as outpatients. Therefore, it may be considered to use one of these criteria in clinical triage based on personal experience and preference [45-47]. The treatment strategies determined by risk classification in PE are summarized in Figure 1 [10].

In conclusion, PE is an important pathology that should be considered in the differential diagnosis of patients presenting with chest pain and shortness of breath in the emergency department. The use of appropriate risk classifications at the time of patient evaluation and the execution of diagnostic

algorithms accompanied by scoring allows the critical patient to be recognized.

In the diagnosis of PE obtained because of the necessary imaging and laboratory tests, making severity estimates and deciding on the need for hospitalization play a key role in effective treatment and management. Reperfusion therapies that should be applied in unstable patients should be planned within the existing experience and facilities and, where possible, should be performed in emergency departments simultaneously with diagnostic processes. Providing an appropriate treatment approach in emergency departments may increase survival.

The prognosis of PE heavily relies on the presence or absence of circulatory collapse and advanced cardiac conditions like cardiac arrest requiring external massage. A comprehensive approach involving swift noninvasive diagnostics, accurate risk assessment, and immediate access to surgical intervention is pivotal for achieving optimal outcomes. Numerous studies have underscored a higher in-hospital mortality rate for patients with preoperative cardiac arrest. Therefore, SPE should

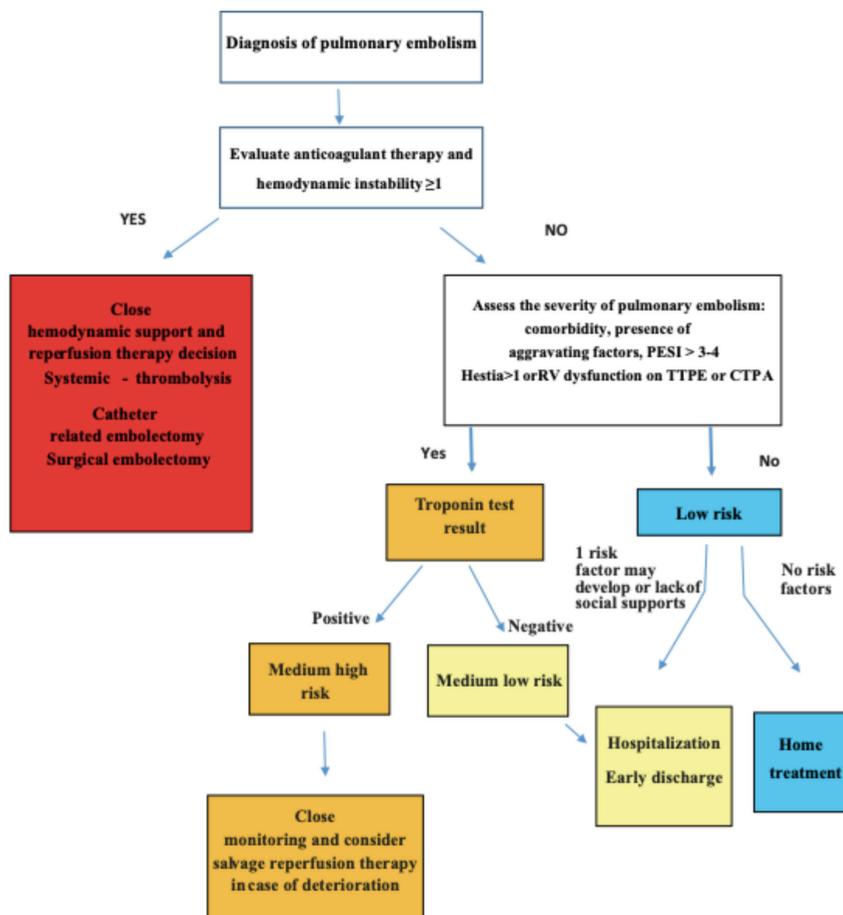


Figure 1. Algorithm including treatment decision stages after the diagnosis of pulmonary embolism

PESI: Pulmonary embolism severity index, RV: Right ventricular, TTPE: Transthoracic echocardiography, CTPA: Computed tomography pulmonary angiography

be considered for patients before progressing to advanced hemodynamic instability and reaching cardiogenic shock.

The growing accessibility of VA-ECMO and concerted efforts to standardize the intricate surgical procedure have significantly enhanced the post-operative outcomes of SPE. This underscores the value of surgery as a viable option for treating PE accompanied by severe RV dysfunction or hemodynamic instability. In the future, there is a pressing need for the reeducation of medical and surgical trainees, ensuring they are well-versed and updated on the role of SPE in acute PE treatment, especially in centers equipped with surgical expertise for performing SPE.

Ethics

Authorship Contributions

Surgical and Medical Practices: M.B., Concept: E.D., A.A., Design: S.E., A.A., Data Collection or Processing: E.D., Analysis or Interpretation: E.D., Literature Search: S.E., Writing: E.D., S.E.

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