Systemic Thrombolysis for Pulmonary Embolism

Evidence, Patient Selection, and Protocols for Management

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KEYWORDS

• Pulmonary embolism • Systemic thrombolysis • Selection of patients • Risk stratification
• Management protocol

KEY POINTS

- Acute pulmonary embolism is associated with significant morbidity and mortality.
- Treatment options include anticoagulation, systemic thrombolysis, catheter-based interventions, and surgical embolectomy.
- Selecting candidates who derive maximal benefit with thrombolysis, while being exposed to the least possible risks of bleeding is difficult.
- Optimal and pragmatic selection of patients should involve a multidisciplinary approach.

INTRODUCTION

Pulmonary embolism (PE) affects 23 per 100,000 people annually,[1] causing morbidity including prolonged hospital stay, recurrence, postthrombotic syndrome, and even mortality. Annual US mortality rates associated with PE are 4 to 5 times greater than those associated with breast cancer or human immunodeficiency virus.[1,2] The incidence of PE rises with increasing age with an associated 1-year mortality approaching 39% in the elderly.[3] It affects hospitalized patients as well as outpatients, with an in-hospital fatality rate of 12%.[1] In spite of recent advances in diagnostic tools, PE remains underdiagnosed and is still considered a diagnostic dilemma, presenting with a wide range of symptoms from mild dyspnea to sudden death. Depending on the likelihood of PE, initial diagnostic tests include D-Dimer, electrocardiogram, cardiac biomarkers, transthoracic echocardiography, computed tomography (CT) scans, and

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ventilation perfusion scans. Based on the results of these tests and hemodynamics of the patient, PE can be categorized into varying grades of clinical severity, each requiring different approaches to management to optimize outcomes.

A major goal of therapy in the management of PE is improvement of hemodynamics by reducing strain on the right ventricle. This can lead to symptom improvement, restoration of pulmonary arterial flow, decreased risk of recurrent PE, and prevention of the development of chronic thromboembolic pulmonary hypertension (CTEPH). Anticoagulation is the cornerstone of therapy for most patients with PE.[4] Patients with high-risk PE or those judged to have a high likelihood of decompensation can be considered for systemic thrombolysis or catheter-based thrombolysis. These therapies may improve symptoms and mortality[4] but place patients at elevated risks of bleeding from their systemic effects. Thrombolytic agents target fibrin via converting plasminogen to plasmin, which breaks down the fibrin,[5] resulting in partial or complete dissolution of clot, rapidly increasing the pulmonary vasculature perfusion. Advances in pharmacotherapy have led to fibrin-specific thrombolytic agents that, unlike first-generation agents (eg, streptokinase), cleave fibrin only by activating plasminogen on the surface of the clot, thus reducing its systemic effects.

RISK STRATIFICATION OF PULMONARY EMBOLISM

Historically, high-risk PE was identified through assessment of embolus burden via invasive angiography using the Miller index,[6] but its use has declined due to its invasive nature. In different studies and registries, hemodynamic instability (hypotension/circulatory shock) has been shown to be the most important determinant of short-term morbidity and mortality,[7] therefore this clinical marker helps to risk-stratify patients with PE. In an American Heart Association (AHA) scientific statement, massive PE was defined as "acute PE with sustained hypotension (systolic blood pressure <90 mm Hg for at least 15 minutes or requiring inotropic support, not due to a cause other than PE, such as arrhythmia, hypovolemia, sepsis, or left ventricular [LV] dysfunction), pulselessness, or persistent profound bradycardia (heart rate <40 bpm with signs, or symptoms of shock)."[4] These patients were considered high-risk. Patients with normal hemodynamics but objective evidence of right heart strain (via imaging or cardiac biomarkers) were called submassive PE, which labeled a patient as intermediate risk in terms of adverse clinical outcomes. This was defined as "acute PE without systemic hypotension (systolic blood pressure ≥90 mm Hg) but with either RV [right ventricular] dysfunction or myocardial necrosis."[4] Patients without hemodynamic instability or evidence of right heart strain were considered low risk.

SELECTION OF PATIENTS FOR SYSTEMIC THROMBOLYSIS

Selecting the correct patient for systemic thrombolysis necessitates a thorough assessment of the patient's preexisting comorbidities, mode of presentation, and focused clinical examination to assess the immediate risk of hemodynamic collapse, the risk of long-term complications, and the risk of major bleeding associated with the thrombolytic agent. As described previously, high-risk PE patients warrant strong consideration of aggressive treatment options including systemic thrombolysis with a high incidence of adverse outcomes if not instituted expediently.[8] In patients who present with acute high-risk PE, the risk of mortality is high, which makes the decision for systemic thrombolysis relatively easier as compared with patients who are hemodynamically stable. The case fatality of these hemodynamically unstable patients ranges from 35% to 58%.[6,9] Therefore, benefits clearly outweigh the risk of adverse outcomes in most patients with high-risk PE who are not experiencing severe active bleeding.[10]

On the contrary, decision making in patients with intermediate-risk PE is more complex, with controversy surrounding the population-based risk of decompensation.[11] Although an analysis of the International Cooperative Pulmonary Embolism Registry in 1999 demonstrated that 15% of hemodynamically stable patients died in first 90 days of diagnosis,[7] a meta-analysis of randomized trials demonstrated only 3% short-term mortality rates in intermediate-risk patients treated with isolated anticoagulation.[10] Close monitoring of these patients is necessary with early administration of thrombolytic agent for "rescue reperfusion" if worsening hemodynamics develop. Thrombolytic therapy is not advisable in patients with low-risk PE due to a clearly unfavorable balance between improving hemodynamics and the elevated risk of intracranial and major bleeding.[12]