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Best Clinical Practice

CURRENT CONTROVERSIES IN THROMBOLYTIC USE IN ACUTE PULMONARY EMBOLISM

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□ **Abstract—Background: Acute pulmonary embolism (PE) has an annual incidence of 100,000 cases in the United States and is divided into three categories: nonmassive, submassive, and massive. Several studies have evaluated the use of thrombolytics in submassive and massive PE. Objective: Our aim was to provide emergency physicians with an updated review of the controversy about the use of thrombolytics in submassive and massive PE. Discussion: Nonmassive PE is defined as PE in the setting of no signs of right ventricular strain (echocardiogram or biomarker) and hemodynamic stability. Submassive PE is defined as evidence of right ventricular strain with lack of hemodynamic instability. Massive PE occurs with occlusive thromboembolism that causes hemodynamic instability. Thrombolysis is warranted in patients with massive PE. Thrombolytic use in submassive PE with signs of right ventricular strain or damage presents a quandary for physicians. Several recent studies have evaluated the use of thrombolytics in patients with submassive PE. These studies have inconsistent definitions of submassive PE, evaluate differing primary outcomes, and use different treatment protocols with thrombolytics and anticoagulation agents. Although significant study heterogeneity exists, thrombolytics can improve long-term outcomes, with decreased bleeding risk with half-dose thrombolytics and catheter-directed treatments. Major bleeding significantly increases in patients over age 65 years. The risks and benefits of thrombolytic treatment—primarily improved long-term outcomes—should be considered on a case-by-case basis. Shared decision-making with the patient discussing the risks and benefits of treatment is advised. Conclusions: Thrombolytic use in massive PE is warranted, but patients with submassive PE require case-by-case analysis with shared decision making. The risks, including major hemorrhage, and benefits, primarily improved long-term outcomes, should be considered. Half-dose thrombolytics and catheter-directed treatment demonstrate advantages with decreased risk of bleeding and improved long-term functional outcomes. Further studies that assess risk stratification, functional outcomes, and treatment protocols are needed. Published by Elsevier Inc.**

□ **Keywords—acute pulmonary embolism; massive; submassive; thrombolytics; thrombolysis**

INTRODUCTION

Acute pulmonary embolism (PE) is a clinical entity with significant morbidity and mortality, with >100,000 cases in the United States annually. The incidence increases with age, from 1 per 1,500 in early life to 1 in 300 per year after age 80 years (1,2). The clinical presentation varies, with up to one-quarter of patients experiencing sudden death, while other patients with large thrombus burden experiencing few or no symptoms (3).

The American Heart Association and European Society of Cardiology classify acute PE into the following categories: nonmassive, submassive, and massive (4,5). Acute management and treatment is based on the patient, vital signs, and signs of clinical shock/instability. Mortality for PE reaches 17% in the first

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3 months, but rates of mortality in massive PE reach 30% to 50% (6–8). Increased mortality is seen in patients older than 70 years, congestive heart failure, chronic obstructive pulmonary disease, cancer, presence of one lung, hypotension, tachypnea, hypoxia, altered mental status, renal failure, prior cerebrovascular accident, right ventricular (RV) dysfunction, and elevated cardiac biomarkers (9–17).

Thrombolysis is an established therapy for massive PE, but the use of thrombolytics for submassive PE is controversial in the literature due to different definitions of submassive PE, different outcomes and definitions of benefit, and the risk of life-threatening hemorrhage (18). This has created a quandary for physicians in the management of submassive PE. Thrombolytic use may reduce intravascular thrombus size and pulmonary resistance; however, there is risk of major bleeding, including intracerebral hemorrhage (ICH). With the risks and benefits present for thrombolytics, the patient should be involved in the decision-making process.

DISCUSSION

Definitions of PE: Massive vs. Submassive

PE severity can be classified utilizing several systems, with prior classifications using anatomic criteria, including >50% obstruction of pulmonary vasculature or occlusion of two or more lobar arteries on computed tomography (CT). Currently, the definition for massive PE centers on hemodynamic instability. The definitions for massive PE, submassive PE, and nonmassive PE are shown in Table 1 (5,19). Of note, guidelines classify acute PE using different nomenclature. The following are the classifications: nonmassive or low risk, submassive or moderate/intermediate risk, and massive or high risk. This article will use nonmassive, submassive, and massive for classification.

Submassive PE accounts for approximately 20% of all PE, with up to 5% in-hospital mortality rate. Morbidity can also be severe, with increased risk of pulmonary hypertension, impaired quality of life, persistent RV dysfunction, and recurrent thrombus formation (17–19).

Table 1. Pulmonary Embolism Definitions and Criteria (4,5,19,20)

Type of Pulmonary Embolism	Definition
Massive	Pulselessness, persistent bradycardia with rate < 40 beats/min and signs of shock or sustained hypotension Sustained hypotension includes systolic blood pressure (SBP) of < 90 mm Hg for >15 min, a SBP of < 100 mm Hg in a patient with a history of hypertension, or a > 40% reduction in baseline SBP. Decrease in blood pressure must not be due to dysrhythmia, hypovolemia, sepsis, or left ventricular (LV) dysfunction
Submassive	Normal or near-normal SBP (≥90 mm Hg) with evidence of cardiopulmonary stress, including right ventricular (RV) dysfunction or myocardial necrosis Defined by RV dilatation on echocardiography (RV diameter divided by LV diameter > 0.9), RV systolic dysfunction on echocardiography, brain natriuretic peptide (BNP) elevation (>90 pg/mL), N-terminal pro-BNP elevation (>500 pg/mL), or electrocardiogram changes (new right bundle-branch block, anteroseptal ST elevation or depression, or anteroseptal T-wave inversion). Myocardial necrosis is defined by elevation in troponin I or T over laboratory normal value or above patient baseline.
Nonmassive	No signs of clinical instability, hemodynamic compromise, or RV strain (echocardiogram or biomarker).

Rationale for Treatment

The primary reasons for treating PE include reduction in time to thrombus resolution, earlier reduction in pulmonary vascular hypertension and right heart strain, decreased recurrence of PE (present thrombus acts as a nidus to further increase clot formation), decreased risk of death, improved functional outcomes, and decreased long-term pulmonary hypertension (4,5). In massive PE and in patients requiring cardiopulmonary resuscitation, thrombolytics can reduce RV pressure, pulmonary artery pressure, improve preload, and improve left ventricular function. These benefits, particularly reduction in mortality, are controversial in submassive PE (21–23). However, utilization of thrombolytics may increase the risk of ICH and other hemorrhage (e.g., intra-abdominal, extremity, and renal), as well as cost (4,5).

Current Guidelines

Several society guidelines comment on the use of thrombolytics in PE. These guidelines for thrombolytic use in patients with PE from the American Heart Association (AHA), American College of Chest Physicians (ACCP), European Heart Association (EHA), and American College of Emergency Physicians (ACEP) are shown in Table 2 (4,5,19,20).

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