Chapter

Thrombolytic Therapy in Pulmonary Thromboembolism

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Abstract

Acute pulmonary thromboembolism (PE) is a common disorder with significant mortality and morbidity. Timely recognition and prompt therapy of this disorder is essential to prevent adverse consequences. Thrombolytic therapy has an important role in the management of high-risk pulmonary embolism patients, where it can be lifesaving. However, the potential clinical benefit of thrombolytic therapy needs to balanced against the risk of major bleeding associated with the use of these agents. Hence patient selection is of paramount importance in determining the success of this therapy. Management strategies in PE are centered around the concept of risk stratification of the cases. In this chapter we briefly discuss the risk categorization of PE cases, followed by a more elaborative discussion of the role of thrombolytic therapy in the management of patients with high risk or intermediate risk PE.

Keywords: pulmonary thromboembolism, embolism, thrombolysis, massive, high risk, sub-massive, intermediate risk, low risk, reperfusion, coronavirus, Covid-19

1. Introduction

Acute pulmonary thromboembolism (PE) is a frequent, often under-diagnosed disease with substantial in-hospital mortality and significant acute as well as long-term morbidity. Worldwide, venous thromboembolism (VTE), comprising of deep vein thrombosis (DVT) and PE, is the third most common acute cardiovascular syndrome after myocardial infarction and stroke [1]. The annual incidence rates of PE vary from 39 to 115 per 100,000 population and of DVT vary from 53 to 162 per 100,000 population, as estimated in epidemiological studies [2, 3]. Following the introduction of widespread use of D-dimer testing and computed tomography pulmonary angiography (CTPA) in 1990s, the estimated incidence of PE has increased significantly. A nationwide time trend analysis from United States has shown a substantial increase in incidence of PE after introduction of CTPA (81% increase, from 62.1 to 112.3 per 100,000) [4]. Other longitudinal studies have shown a similar trend with increased rates of PE over time [5]. The overall incidence rates of PE are higher in males as compared to females (56 versus 48 per 100,000, respectively) [6, 7]. The incidence rates increase exponentially with increasing age, especially in women, such that rates are nearly eight times higher in individuals aged >80 years than in the fifth decade of life [2].

Pulmonary embolism ranks third among the causes of cardiovascular death, after myocardial infarction and stroke [3]. It is one of the leading preventable causes of death in hospitalized patients. In the United States, PE is responsible for nearly 100,000 deaths annually [3, 6–9]. Data from six European countries with

a total population of 454.4 million, has shown that in 2004, more than 370,000 deaths were related to VTE [8]. Of these, 34% died abruptly, or within the first few hours of an acute event, before treatment could be started or take effect. In other patients, mortality resulted from acute PE that was diagnosed after death in 59% and in only 7% of the patients who died early, the correct diagnosis of PE was made before death [8]. Time trend analyses from North American, European, and Asian populations have suggested that case fatality rates of acute PE may be declining [3, 10–15]. This positive impact on prognosis of acute PE appears to be related to more widespread use of effective therapies and interventions in the recent years [16, 17].

Prognosis from acute PE is related to the degree of obstruction and its hemodynamic consequences. According to its severity, PE is usually divided into 3 categories as proposed by American Heart Association (AHA) and European Society of Cardiology (ESC) guidelines [18, 19]:

1. Massive (AHA) or high risk (ESC) PE: these hemodynamically unstable patients are characterized by the presence of cardiac arrest or persistent hypotension [defined as a systolic blood pressure (SBP) <90 mmHg and/or a fall in SBP of >40 mmHg for at least 15 minutes, or needing vasopressor support], with or without the evidence of end organ hypo-perfusion. These patients account for nearly 5% of hospitalized PE patients and have an average one-month mortality of around 30% [20].

2. Sub-massive (AHA) or intermediate risk (ESC) PE: These patients are identified by the presence of right ventricle (RV) strain without hypotension. RV strain includes RV dysfunction on echocardiography or CTPA [right/left ventricular (LV) ratio > 0.9] or RV injury and pressure overload with an increase in the level of cardiac biomarkers like troponins or brain natriuretic peptide (BNP). There are some differences in the AHA and ESC guidelines pertaining to this category of patients. The criterion for sub-massive PE in AHA guidelines is the presence of RV strain without hypotension. The ESC criteria of intermediate-risk PE are more broader and include patients with a simplified Pulmonary Embolism Severity Index (sPESI) score ≥ 1 (i.e., age > 80 years; cancer, chronic heart failure or chronic pulmonary disease; heart rate > 110 bpm; SBP <100 mm Hg; or arterial oxygen saturation < 90%), regardless of presence of RV strain. The ESC further subcategorizes these patients into 2 sub-groups depending on the presence of both RV dysfunction and RV injury (intermediate risk—high) or only one or neither of these (intermediate risk—low). These patients with sub-massive or intermediate-risk PE constitute about 35–55% of hospitalized PE patients and the short-term mortality rates in this heterogeneous group vary from 2 to 3% over a period of 7 to 30 days in prospective randomized clinical trials [21], to 3–15% over a period of 7 to 90 days in observational cohort studies [22–24].

3. Low risk (AHA and ESC) PE: These are the patients of PE who do not meet the criteria for sub-massive (AHA) or intermediate-risk (ESC) PE. These account for 40–60% of hospitalized PE patients and have an estimated mortality of around 1% within 1 month [25].

Timely risk stratification of a patient with acute PE is essential for determining the optimal therapeutic approach. Low risk PE patients are typically managed with anticoagulation alone. In massive or high-risk PE patients and some selected high-risk patients in the sub-massive or intermediate risk category early reperfusion therapy is the need of hour, which can be lifesaving. Primary reperfusion therapy

in most cases is systemic thrombolysis. Alternative reperfusion therapies include surgical embolectomy or percutaneous catheter-directed treatments, which are primarily used in patients with contraindications to systemic thrombolysis, depending upon the local availability and expertise [19]. In the following sections, we discuss the role of systemic thrombosis in the treatment of acute PE.

2. Use of thrombolytic therapy in acute pulmonary embolism

2.1 Decision to thrombolyse

In pulmonary embolism, thromboembolic obstruction of the pulmonary arterial tree with the resultant increase in right ventricular afterload is the central pathophysiologic process leading to the development of hemodynamic instability and possible mortality. Rapid removal of the clot, either pharmacologically or surgically results in prompt restoration of pulmonary circulation and decrease in pulmonary arterial pressures [26]. Thrombolysis has been shown to result in more rapid restoration of pulmonary perfusion as compared to anticoagulation alone, with resultant improvement in hemodynamics and right ventricular function. This positive impact of thrombosis on hemodynamics is limited to the initial few days. In patients surviving acute PE, these differences are no longer noted at one week after the therapy [27].

Decision to thrombolyse a patient with acute PE is of critical importance which requires a good judgment about the benefit–risk ratio of thrombolytic therapy. Instituting thrombolytic therapy in a sick patient with persistent hypotension or shock who is at low bleeding risk can prevent a potential mortality; whereas its use in an intermediate risk patient with high bleeding risk can have devastating bleeding consequences. Given the inherent difficulties in this decision making, many centers and society guidelines have advocated the formation of Pulmonary Embolism Response Teams (PERTs) for the management of high risk and selected cases of intermediate risk PE patients [19]. These teams could consist of specialists from different fields like cardiology, pulmonary, intensive care/anesthesiology, hematology, cardiac surgery, vascular medicine and interventional radiology, depending upon the local availability. This facilitates timely decision making in a particular case, with quick formulation of a treatment strategy and its implementation.

Thrombolysis is typically considered in a hemodynamically unstable patient who has a confirmed or highly suspected acute PE and who has a favorable risk–benefit ratio with a low bleeding risk. Diagnosis is usually made on the basis of findings of CTPA, although, ventilation-perfusion scans or catheter pulmonary angiography can also be confirmatory. Sometimes, the thrombolytic therapy is instituted on making the diagnosis by a bedside echocardiogram when patient is too sick to be shifted for CTPA or if it is not available immediately. Very infrequently, thrombolytic therapy may be started during cardiopulmonary resuscitation in a patient with high clinical suspicion of PE, although it is rarely effective in cases of refractory pulseless activity arrest.

Thrombolysis in PE is most effective when stated within 48 hours of symptom onset, but can still be potentially useful for up to 14 days of symptom onset in selected patients [19].

2.2 Thrombolysis in massive or high-risk PE

The most widely accepted indication of thrombolysis in acute PE is the presence of high risk or massive PE [18, 19, 28, 29]. These recommendations are supported by

the findings of a small randomized controlled trial which compared thrombolytic therapy (streptokinase) followed by heparin or heparin alone in eight patients with massive PE. In this study, the thrombolytic therapy was found to be associated with significant reduction in mortality as compared to heparin alone [30].

2.3 Thrombolysis in sub-massive or intermediate risk PE

Thrombolysis in this category of PE is controversial and often requires an individualized approach to the patient. The current evidence does not support the routine use of thrombolytic therapy in these patients, although rescue thrombolysis is indicated in patients who have hemodynamic deterioration while being treated with anticoagulants [18, 19, 28, 29].

Nevertheless, thrombolysis in these patients has been associated with reduced chances of hemodynamic compromise and possibly, reduced risk of long-term complications including chronic thromboembolic pulmonary hypertension (CTEPH) [31], albeit, at the cost of increased bleeding events including intracranial hemorrhage.

There have been many studies which have tried to explore the role of thrombolytic therapy in this group of patients. The largest among these is the Pulmonary Embolism Thrombolysis (PEITHO) trial, a randomized double blind trial of 1005 patients [31]. It randomized normotensive patients with intermediate risk PE to either tenecteplase plus heparin or placebo plus heparin. To be eligible for this trial, the intermediate risk PE patients needed to have evidence of right ventricular dysfunction on echocardiography or CTPA along with elevated levels of cardiac troponins. The primary outcome of death or the development of hemodynamic compromise within 7 days occurred in 2.6% of the patients in tenecteplase group as compared to 5.6% in the placebo group (odds ratio, 0.44; 95% confidence interval, 0.23 to 0.87; $p = 0.02$). Up to 7 days of randomization, the mortality was not significant different between the groups (1.2% in tenecteplase group vs. 1.8% in placebo group, $p = 0.42$). The benefit of decreased primary outcome in this study came at the cost increased risk of major extra-cranial (6.2% in tenecteplase group vs. 1.2% in placebo group, $p < 0.001$) and intra-cranial bleeding (2% in tenecteplase group vs. 0.2% in placebo group, $p = .003$). On follow-up of up to 30 days, the death rate was not statistically significant between the groups (2.4% in tenecteplase group vs. 3.2% in placebo group, $p = 0.42$). Thus, in this study thrombolytic therapy decreased the incidence of development of hemodynamic compromise but had no impact on 7 days and 30 days mortality.

Other studies conducted in this field have been limited by smaller sample size of the study population, thus necessitating the use of composite outcome end-points. The management strategies and prognosis of pulmonary embolism (MAPPET-3) trial randomized 256 normotensive PE patients with pulmonary hypertension or RV dysfunction to receive either heparin plus alteplase or heparin plus placebo. The primary outcome of in-hospital mortality or clinical deterioration requiring an escalation of treatment, was significantly lower in thrombolytic group (11% vs. 24.6%, $p = 0.006$), and the thrombolytic group had higher the probability of 30-day event free survival by Kaplan-Meir estimates ($p = 0.005$). The difference in the primary outcome was largely due to higher number of patients in the heparin group requiring escalation of the treatment, with no significant difference in mortality. The incidence of fatal bleeding or hemorrhagic stroke was not significantly different between the groups [32]. Moderate Pulmonary Embolism Treated with Thrombolysis (MOPETT Trial) randomized 121 patients with moderate PE to receive low dose thrombolytic therapy plus anticoagulation or anticoagulation alone. In this study, the thrombolytic therapy was associated with a significant reduction of pulmonary hypertension which was maintained up to

28 months, although there was no difference in mortality [33]. The North American Tenecteplase or Placebo: Cardiopulmonary Outcomes at Three Months (TOPCOAT) trial also explored the use of thrombolytic therapy in patients with sub-massive PE [34]. This study had different design as compared to the contemporary PEITHO trial with broader definition of submissive PE which allowed inclusion if there was evidence of RV hypokinesis on echocardiography or there were elevated cardiac biomarkers (cardiac troponin I/T or BNP/NT-pro BNP). This trial had to be prematurely terminated due to relocation of the principal investigator and thus only 83 patients could be randomized. The primary outcome at 5 days (a composite of death, circulatory shock, intubation, or major bleeding) was seen in one patient in thrombolytic arm and three patients in the heparin arm.

There have been many systematic reviews and meta-analyses published regarding the use of thrombolysis in patients with sub-massive or intermediate PE. One such analysis by Chatterjee et al. in 2014, included 16 RCTs with 2115 patients of both massive (or high risk) and sub-massive (or intermediate risk) PE patients. This analysis reported a lower all-cause mortality in thrombolytic group (odds ratio 0.53, 95% confidence intervals 0.32–0.88), although with a greater risk of major bleeding (odds ratio 2.73, 95% confidence intervals 1.91–3.91). In a sub-set of 1775 patients from 8 trials of intermediate risk PE, it was noted that systemic thrombolytic therapy was associated with reduction in mortality in intermediate high-risk PE patients with RV dysfunction as compared to anticoagulation alone (odds ratio 0.48, 95% confidence intervals 0.25–0.92), but at the cost of increased major bleeding events (odds ratio 3.19, 95% confidence intervals 2.07–4.92) [21]. A recently published meta-analysis by Zuo et al. in 2021, included 21 trials with a total of 2401 patients with both stable and unstable PE. The results showed that thrombolytic therapy followed by heparin was associated with lower risk of death (odds ratio 0.58, 95% confidence intervals 0.38–0.88) and recurrent PE (odds ratio 0.54, 95% confidence interval 0.32–0.91). However, the evidence was of low certainty for both of these outcomes as the effects weakened significantly after the exclusion of one study with high risk of bias. Thrombolytic therapy was associated with higher risk of major bleeding (odds ratio 2.84, 95% confidence intervals 1.92–4.20) and hemorrhagic stroke (odds ratio 7.59, 95% confidence intervals 1.38–41.72) [35].

Given the equivocal nature of the clinical evidence till date, the decision to thrombolyse a patient with sub-massive or intermediate PE should be individualized with careful consideration of the benefit–risk ratio. The AHA 2011 guidelines support the use of thrombolytic therapy in sub-massive PE cases who have clinical evidence of adverse prognosis (new hemodynamic instability, deteriorating respiratory failure, severe RV dysfunction, or major myocardial necrosis) and low risk of bleeding (Class IIb; Level of Evidence C) [18]. The 2016 CHEST guidelines recommend against the use of thrombolytic therapy in acute PE without hypotension (grade 1B) [28]. Similarly, the ESC 2019 guidelines and 2020 American Society of Hematology (ASH) guidelines recommend against the routine use of thrombolytic therapy in patients with intermediate risk or sub-massive PE [19, 29].

2.4 Thrombolytic agents and their dosing

The approved thrombolytic agents and their dosing in PE has been shown in **Table 1**.

To date, no studies have been shown the superiority of one agent over the other in this patient population. The ease of administration coupled with the non-availability of first-generation agents (streptokinase and urokinase), has made recombinant tissue-plasminogen activator (rt-PA, alteplase) as the favored agents in most of the developed world; however, given their lower costs, the first-generation agents are still

Drug	Dose
Recombinant tissue-plasminogen activator (rt-PA)	100 mg in 2 hours, accelerated regimen 0.6 mg/kg over 15 mins (maximum dose 50 mg)
Streptokinase	250,000 IU loading dose over 30 mins, followed by 100,000 IU/h for 12–24 h; accelerated regimen 1.5 million IU over 2 h
Urokinase	4400 IU loading dose over 10 mins, followed by 4400 IU/kg/h over 12–24 h; accelerated regimen: 3 million IU over 2 h

Table 1.
Approved thrombolytic agents and their dosing in pulmonary embolism [19].

widely used in the developing world. Unfractionated heparin (UFH) may be continued during the infusion of rt-PA but it should be with-held during the infusion of streptokinase or urokinase [19]. Other investigational thrombolytic agents for use in PE include tenecteplase, reteplase, desmoteplase, but none has been approved as yet [19].

2.5 Contraindications to thrombolysis

The major contraindications to thrombolytic therapy are listed in **Table 2**.

Absolute contraindications
• History of hemorrhagic stroke or stroke of unknown origin
• Ischemic stroke in last 6 months
• Intracranial neoplasm or structural cerebral vascular lesion
• Major trauma, surgery or head injury in last 3 weeks
• Active bleeding (excluding menstrual bleeding)
• Bleeding diathesis
• Suspected aortic dissection
Relative contraindications
• Severe uncontrolled hypertension (systolic BP >180 mm Hg or diastolic BP >110 mm Hg)
• History of poor controlled hypertension in the past
• Transient ischemic attack in last 6 months
• Current use of oral anticoagulants
• Pregnancy or first week post-partum
• Non-compressible vascular puncture sites
• Age more than 75 years
• Advanced liver disease
• Active peptic ulcer disease
• For streptokinase or urokinase: previous exposure (more than 5 days ago) or previous allergic reaction to these agents

Table 2.
Contraindications to thrombolysis [18, 19].

2.6 Assessment of response to therapy

This is usually done by continued clinical monitoring of the patient for improvement in signs and symptoms (e.g., improved blood pressure, reduced respiratory

rate or heart rate, improvement in oxygenation). Some centers advocate serial echocardiograms to evaluate for improvements in pulmonary artery pressures and RV dysfunction. Although RV size and function may improve acutely, but often it may lag behind the signs of clinical improvement by several weeks to months. After thrombolytic therapy the patient is transitioned to long term anticoagulant therapy depending upon the etiology.

2.7 Role of low dose thrombolytic therapy

The disappointingly high rates of intra-cranial hemorrhage in the PEITHO trial, led many investigators to explore the use of low-dose thrombolytic therapy in patients with PE. The widely recommended rt-PA dose of 100 mg over 2 hours is largely based from experience from the patients with myocardial infarction. Many researchers have argued that lungs may be an organ with higher sensitivity to thrombolytic therapy as compared to the myocardium and given that lungs receive the entirety of cardiac output as compared to only 5% being received by the coronary circulation, low-dose thrombolytic therapy in PE seems to be a logical approach. Low-doses thrombolytic therapy could be especially useful in elderly patients, pregnant patients and in those who have relative contraindications.

A multicenter RCT by China VTE group published in 2010, randomized 118 patients with either hemodynamic unstable or anatomic massive pulmonary obstruction to full dose (100 mg/2 h) rt-PA regimen or half dose (50 mg/h) rt-PA regimen. Half-dose regimen was associated with similar improvements in RV function, lung perfusion defects and pulmonary artery obstruction, and had lesser bleeding complications especially in patients with body weight of less than 65 kgs [36]. The subsequent MOPETT trial (as described above) published in 2013, demonstrated significant lower risk of progressive pulmonary hypertension in low-dose thrombolytic arm, albeit with a similar mortality [34]. Another study of 66 patients with intermediate risk PE, randomized patients to receive either low dose rt-PA (30 mg/2 h) plus low-molecular weight heparin (LMWH) or LMWH alone. In this study, the thrombolytic group had significant reductions in pulmonary artery systolic pressures (PASP) and the RV/LV ratio as compared to the baseline. There was no significant change in these parameters from the baseline in LMWH group. Thrombolytic therapy resulted in significant decrease in PASP and an improved symptom severity as compared to LMWH group. On follow up of 90 days, no significant difference was noted in terms of mortality, recurrent venous thromboembolism or major bleeding, although, thrombolytic group had more minor bleeding and less hemodynamic decompensation [37]. In a recently published prospective, non-randomized open label, single center study of 76 patients with intermediate risk PE, half dose rt-PA (50 mg/2 h) plus LMWH was compared to LMWH alone. It was found that half dose rt-PA significantly prevented mortality or hemodynamic deterioration at 7 days and 30 days without increase in bleeding risk [38]. Thus, the results from these small studies suggest that low dose thrombolytic therapy may be an attractive option in the treatment of PE, however, larger RCTs are needed to draw definite conclusions on this topic.

2.8 Thrombolysis in pulmonary embolism related to Covid-19

Coronavirus disease-19 (Covid-19) is associated with a significantly increased risk of procoagulant events including PE, the risk being highest in critically ill patients with severe disease admitted to intensive care units (ICUs) [39]. The development of PE in patients with Covid-19 is associated with worse outcomes, mandating quick recognition and prompt management [40]. In the absence of

robust data from large studies, the Global COVID-19 Thrombosis Collaborative Group currently advocates managing PE in Covid-19 on the similar lines as patients of non-Covid PE [41]. Systemic thrombolysis is recommended for patients with Covid-19 related PE in case of massive or high-risk PE; or in patients with sub-massive or intermediate PE who develop hemodynamic deterioration while being treated with anticoagulant therapy. However, there are few peculiarities of this situation which demand careful consideration. Firstly, it is often difficult to disentangle the hemodynamic consequences of PE in a sick Covid-19 patient from those of severe pneumonia and acute respiratory distress syndrome (ARDS); thus, necessitating critical thinking and judgment. Secondly, Covid-19 is often associated with an unfamiliar coagulopathy with the presence of thrombocytopenia in a sizeable proportion of the patients which increases the risk of bleeding complications from systemic thrombolysis [42]. Presence of co-existent thrombocytopenia calls for an individualized approach in such patients and many researchers have advocated the use of catheter directed thrombolysis as the potential first line therapy in these patients [43]. Further evidence from larger studies is needed in this field to guide decision making.

3. Conclusions

Acute PE is a frequent disorder which needs timely recognition and management to ensure good outcomes. Thrombolytic therapy plays a central role in the management of patients with massive (or high-risk) PE, where it can be lifesaving. This therapy can also be useful in improving outcomes in carefully selected patients with sub-massive (or intermediate risk) PE.

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