Potential role of systemic thrombolysis in acute submassive intermediate risk pulmonary embolism: review and future perspectives

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Abstract: Submassive (intermediate risk) pulmonary embolism (PE) continues to be a significantly morbid disease process that remains unrecognized, inadequately risk stratified and suboptimally treated. Appropriate early clinical and imaging-based risk stratification represents the cornerstone for adequate therapeutic decision making, particularly for the selection of candidates who may benefit the most from systemic thrombolysis. The relevance of estimating clinical prognostic scores, in combination with imaging data, for accurate assessment of right ventricular function and laboratory biomarkers, indicative of myocardial injury for identification of normotensive patients at intermediate risk for an adverse short-term outcome are emphasized in this review. Recent clinical trials have demonstrated improvement in hemodynamics and mortality with the use of systemic thrombolysis among intermediate risk patients; however, it came at the cost of a significantly increased risk of major bleeding. Catheter-based therapies have garnered considerable clinical interest in recent years; of particular note is the ultrasound accelerated catheter-directed thrombolysis which has emerged as a novel and attractive alternative therapeutic modality with an increasing number of single center studies and ongoing randomized trials. Our review focuses on the major trials and studies involved in submassive PE in the recent literature including the role of thrombolytic therapy. We include major trials with reasonable sample size and extensive review of the potential side effects, such as major bleeding.

Keywords: clinical outcomes, right ventricular dysfunction, risk stratification, submassive pulmonary embolism, systemic thrombolysis

Introduction

Acute massive pulmonary embolism (PE) is one of the most frequent and lethal cardiovascular events, associated with an almost 95% mortality rate. This clinical presentation requires an aggressive therapeutic and cardiopulmonary resuscitative strategy such as systemic thrombolysis, catheter-based therapies or surgical embolectomy [Goldhaber *et al.* 1999; Jaff *et al.* 2011]. Studies have demonstrated that acute PE induced right ventricular (RV) failure is the most common cause of a 30-day mortality rate [Jaff *et al.* 2011; Wood, 2002]. The hemodynamic status is the best prognostic factor to determine implication

for short-term mortality in acute PE patients. Massive PE is characterized by persistent arterial hypotension and/or cardiogenic shock with an increased short-term mortality rate [Wood, 2002]. Table 1 lists shows specific echocardiographic objective signs of RV dysfunction.

Acute submassive PE is defined by the presence of normotensive patients with signs of RV dysfunction and/or myocardial injury with a short-term mortality rate ranging from 3% to 15%. Table 2 shows our proposed definition criteria of acute severe submassive PE; the best therapeutic approach for submassive PE remains controversial

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Table 1. Echocardiographic criteria for RV dysfunction.

Qualitative criteria: RV hypokinesis (mild, moderate, severe)		
Quantitative criteria	RV dilation	Pulmonary hypertension
	RV:LV end diastolic diameter >1 RV end-diastolic diameter >30 mm	Pulmonary artery systolic pressure >30 mmHg. Tricuspid regurgitant velocity >2.8 m/s Pulmonary artery mean pressure >20 mmHg
LV, left ventricle; RV, right ventricle.		

Table 2. Proposed diagnostic definition of severe acute submassive pulmonary embolism.

Definition	Echocardiographic findings	BNP	EKG	Elevated troponin I
Systolic blood pressure >90 mmHg and RV dysfunction or myocardial necrosis defined by one of the following.	RV dilation (apical 4-chamber RV diameter divided by LV diameter >0.9) or RV systolic dysfunction on echocardiography or RV dilation (4-chamber RV diameter divided by LV diameter >0.9) on CT	Elevation of BNP (>90 pg/ml), or N-terminal pro-BNP (>500 pg/ml)	EKG changes (new complete or incomplete right bundle branch block, anteroseptal ST elevation or depression, or anteroseptal T wave inversion)	Troponin I (>0.4 ng/ml) or troponin T (>0.1 ng/ml)
BNP, brain-type natriuretic peptide; CT, computed tomography; EKG, electrocardiogram, LV, left ventricle; RV, right ventricle.				

[Ince *et al.* 2014; Porres-Aguilar and Porres-Muñoz, 2014]. Patients presenting as hemodynamically stable could have a similar short-term mortality risk as those with massive PE if they are appropriately assessed as clinically risk stratified early on (Table 3), eventually leading to more applicable and aggressive therapies [Kucher *et al.* 2005; Sanchez *et al.* 2008; Schoepf *et al.* 2004; Becattini and Agnelli, 2008]. Although systemic thrombolysis has demonstrated hemodynamic and angiographic improvements compared with standard intravenous (IV) heparin in patients with massive PE, studies have not provided clear evidence in regard to the clinical outcomes such as morbidity and mortality; however, there has been a noteworthy trend towards reduction in PE-related mortality and recurrent PE episodes [Kucher *et al.* 2006; Jerjes-Sanchez *et al.* 1995; Stein and Matta, 2012; Wan *et al.* 2003]. Figure 1 shows an integrated multidisciplinary therapeutic approach in sub massive PE.

Clinical investigations have explored the potential role of systemic thrombolysis in acute severe submassive PE following an adequate integrated

risk-stratification (Figure 2). The common risk stratification approach includes evidence of objective RV dysfunction detected by transthoracic echocardiography (TTE), chest computed tomographic angiography (CTA), elevated cardiac injury biomarkers such as troponin-I, brain natriuretic peptide (BNP) and pro-BNP. An additional approach includes cardiopulmonary clinical status such as moderate or severe hypoxemia by oxygen saturation (O₂Sat) and arterial partial pressure of oxygen (PaO₂) [Tapson, 2013; Jiménez, 2013; Lankeit and Konstantinides, 2012].

The question remains whether the indication of systemic thrombolysis could positively impact the clinical outcomes, e.g. survival, quality of life and the development of persistent pulmonary arterial hypertension (PAH) in the subgroup of patients with submassive PE. This review focuses on current evidence of clinical trials and the management of submassive PE; other possible treatment modalities such as catheter-based therapies using local thrombolysis or direct extraction/embolectomy have been excluded.

Table 3. Pulmonary Embolism Severity Index.

Prognostic variables	Points assigned
Demographics	
Age (years)	Age
Male sex	+10
Comorbid conditions	
Cancer	+30
Heart failure	+10
Chronic lung disease	+10
Critical findings	
Pulse >110 beats per minute	+20
Systolic blood pressure <100 mm Hg	+30
Respiratory rate >30 breaths per minute	+20
Temperature <36°C	+20
Altered mental status*	+60
Arterial oxygen saturation <90% [§]	+20
Class I (very low risk: 65 points, mortality 0–1.6%).	
Class II (low risk: 66–86 points, mortality 1.7–3.5%).	
Class III (intermediate risk: 86–105 points, mortality 3.2–7.1%).	
Class IV (high risk: 106–125 points, mortality 4–11.4%).	
Class V (very high risk: >125 points, mortality 10–24.5%).	
*Disorientation, lethargy, stupor, or coma.	
[§] With or without supplementary oxygen.	

Current evidence of clinical trials evaluating systemic thrombolysis in acute submassive PE

Meta-analysis evaluation

Chatterjee and colleagues published a meta-analysis consisting of 16 clinical trials including 2115 patients [Chatterjee *et al.* 2014]. These studies were randomized clinical trials comparing systemic thrombolytic therapy *versus* standard anticoagulation therapy. The results indicated a decreased all-cause mortality [odds ratio (OR), 0.53; 95% confidence interval (CI), 0.32–0.88; 2.17% *versus* 3.89% with anticoagulants; number needed to treat (NNT)=59 with absolute risk reduction of 1.12%]. The risk of major bleeding was noted to be greater [OR, 2.73; 95% CI, 1.91–3.91; 9.24% *versus* 3.42%; number needed to harm (NNH)=18]. Thrombolysis was noted to have a lower risk of recurrent PE (OR, 0.40; 95% CI, 0.22–0.74; 1.17% *versus* 3.04%; NNT=54). A lower mortality rate was observed in submassive PE trials (OR, 0.48; 95% CI, 0.25–0.92) [Lankeit and Konstantinides, 2012]. Nakamura and colleagues conducted a similar meta-analysis that included 6 randomized control trials consisting of 1510 patients; the results were

Figure 1. Proposed algorithm treatment for the management of submassive pulmonary embolism. CDT, catheter directed therapy; IVC, inferior vena cava.

Figure 2. Proposed algorithm for risk stratification of acute pulmonary embolism.

CTA, computed tomography angiography; EKG, electrocardiogram; PE, pulmonary embolism; PESI, pulmonary embolism severity index; RV, right ventricle; TTE, transthoracic echocardiogram.

similar to that of Chatterjee and colleagues [Chatterjee *et al.* 2014]. However, there was a slightly larger absolute risk difference (1.6%), although this was not significant due to the smaller sample size [Nakamura *et al.* 2014].

Management Strategies and Prognosis of Pulmonary Embolism Trial-3 (MAPPET-3) trial

Konstantinides and colleagues evaluated a multi-center, randomized, double-blind, placebo controlled trial in Germany [Konstantinides *et al.* 2002]. It consisted of 256 patients with submassive PE and objective evidence of PAH or RV dysfunction without hypotension or shock. Patients received either IV heparin plus IV 100 mg of alteplase (118 patients) *versus* IV heparin plus placebo (138 patients) over a 2-hour time span. The primary endpoint was to evaluate in-hospital death rates or clinical outcomes requiring an increased dosage of therapy. The secondary

endpoint was to evaluate safety and tolerability. The incidence of the primary endpoint was higher among the heparin patients and placebo group ($p = 0.006$). It was noted also that the 30 days' event-free survival rate was higher in the heparin plus alteplase group ($p = 0.005$). This difference was directly attributed to a higher incidence of increased therapy in the heparin plus placebo group (24.6% *versus* 10.2%), with both groups evidencing low mortality rates (3.4% in the heparin plus alteplase group *versus* 2.2% in the heparin plus placebo group, $p = 0.71$). A significant finding, resulting from the research, was nonfatal or intracranial hemorrhage occurring in the heparin plus alteplase group *versus* one fatal bleeding episode in the heparin plus placebo group. The investigators concluded that alteplase plus heparin in submassive PE can improve clinical outcomes in otherwise stable patients; it can also prevent deteriorated clinical condition if escalation of treatment is needed.

Tenecteplase Italian Pulmonary Embolism Study (TIPES)

This was a multi-center, randomized, double-blind, placebo-controlled study where Becattini and colleagues evaluated the effect of IV tenecteplase on RV dysfunction as assessed by echocardiogram in hemodynamically stable patients with submassive PE as the primary endpoint [Becattini *et al.* 2010]. The study included a total of 58 patients; however, the echocardiogram was adequate for only 51 analyses. It was estimated that 23 patients were randomized to tenecteplase and 28 to placebo. Tenecteplase was given as a weight-adjusted bolus at a dose ranging between 30 and 50 mg, and all patients in the study received unfractionated heparin. The reduction of the RV to LV end-diastolic dimension ratio at 24 hours was statistically significant (0.31 ± 0.08 in the tenecteplase group *versus* 0.10 ± 0.07 in placebo, $p = 0.04$). Adverse events were noted as follows: two nonfatal bleeding occasions occurred in the tenecteplase group (one intracranial) and one episode in the placebo group; one patient had recurrent PE in the tenecteplase group *versus* three patients in the placebo group. The study also evaluated the 30 days' mortality rate which included 1 patient in the placebo group who died of myocardial infarction (MI). No further recurrent venous thromboembolism event or death occurred until day 30. The NNH, related to clinical events at 30 days, was noted to be 58.5 specifically with regard to death as we calculated that value. The investigators concluded that IV bolus weight-adjusted tenecteplase was associated with improvement of RV dysfunction at 24 hours; whether this benefit is associated with improvement in survival without excessive bleeding events still remains to be defined.

Moderate Pulmonary Embolism Treated with Thrombolysis Trial (MOPETT)

The study reflected a prospective, randomized, controlled, single-center open approach headed by Sharifi and colleagues where the effect of a 'safer dose' of recombinant tissue plasminogen activator (rTPA) as the choice of thrombolytic agent in the reduction of pulmonary arterial pressure in 'moderate' PE was evaluated [Sharifi *et al.* 2013]. The investigators defined 'moderate' PE as the presence of classic features of acute PE plus chest CTA involvement of >70% of thrombus in >2 lobar arteries. They also extended the definition to the involvement of the main right or left pulmonary arteries or by a ventilation/perfusion

lung scan showing high probability PE in ≥ 2 lobes. The primary endpoint of the study was to evaluate the development of PAH and its endpoint, and also to evaluate recurrent PE at 28 months. The secondary endpoint was to evaluate total mortality, hospital stay duration, bleeding, recurrent PE and mortality with recurrent PE combined factors. About 121 patients were randomized to either IV rTPA ($n = 61$) at 50 mg in those weighing >50 kg or 0.5mg/kg if <50 kg plus anticoagulation (unfractionated heparin or subcutaneous enoxaparin). The other arm of the study was to randomize patients to receive anticoagulation therapy (control group, $n = 60$) over a period of 22 months. PAH developed in 9 of 58 patients (16%) in the thrombolysis plus anticoagulation group compared with 32 of 57 patients (57%) in the control group. The composite endpoint of PAH developed in 9 of 58 patients (16%) in the thrombolysis plus anticoagulation group compared with 35 of 56 patients (63%) in the control group. Secondary endpoint evaluation revealed the following. Hospital duration was 2.2 ± 0.5 days in the thrombolysis plus anticoagulation group *versus* 4.9 ± 0.8 days in the control group; the combination between death and recurrent PE was 1 (1.6%) in the thrombolysis plus anticoagulation group *versus* 6 (10%) in the control group ($p = 0.048$); no bleeding episodes noted in all groups. Some variations noted in terms of NNT/NNH were 2.1 and 11.9 respectively. The investigators concluded that a 'safe dose' of rTPA was adequate and effective with a reduction in pulmonary arterial pressures as a possible alternative for the same dose when used in a catheter related thrombolysis approach.

Pulmonary Embolism Thrombolysis (PEITHO) trial

In this prospective, multi-center, international, randomized, double-blind, placebo controlled study with the overall goal of comparing thrombolysis with IV Tenecteplase in normotensive patients with acute submassive PE *versus* placebo ($n = 1006$), all study subjects received anticoagulation [Meyer *et al.* 2014]. The primary endpoint was to evaluate all-cause mortality or hemodynamic collapse within 7 days of randomization. The secondary endpoint focused on assessing the safety of tenecteplase such as nonintracranial bleeding, strokes within 7 days and serious adverse events. Although the primary outcome of all-cause mortality or hemodynamic collapse occurred in 13 patients (2.6%) randomized to the IV tenecteplase

group compared with 28 patients (5.6%) randomized to placebo ($p = 0.015$), there were more major nonintracranial bleeding events with 32 patients (6.3%) in the IV tenecteplase arm compared with 6 patients (1.5%) in the placebo arm. All strokes were noted to be higher in the T=tenecteplase arm (12 patients, 2.4%) *versus* placebo (1 patient, 0.2%). In contrast to these findings, serious adverse events were lower in the tenecteplase arm (29 patients, 5.7%) *versus* placebo (39 patients, 7.8%). Another observed finding was the all-cause mortality within 30 days of randomization was lower in the tenecteplase arm (12 patients, 2.4%) *versus* placebo (16 patients, 3.2%). The study also evaluated a specific subgroup defined by age (<75 years *versus* >75 years). NNH from these subgroups included major extracranial bleeding and was noted to be 38.5 in subgroup patients <75 years and 9.5 in those >75 years old. The authors concluded that, in patients with appropriate integrated prompt risk stratification for submassive (intermediate risk) acute PE, IV tenecteplase significantly reduced the primary endpoint of death or hemodynamic collapse within 7 days of randomization. They also confirmed that early systemic thrombolytic therapy prevents RV dysfunction and myocardial injury. The trial also addressed that secondary thrombolysis, after clinical deterioration, is very effective and likely the most reasonable approach in patients with submassive PE. One of the major negative points from this trial included the significant increased risk of major bleeding events, specifically intracranial bleeding in elderly patients (>75 years old).

Other studies

Riera-Mestre and colleagues conducted a retrospective cohort study of 15,944 patients with symptomatic acute PE identified from the multi center, international, prospective, Registro Informatizado de la Enfermedad TromboEmbólica (RIETE registry). The main goal was to evaluate the all-cause mortality during the first 3 months after the diagnosis of a PE. In the normotensive subgroup patients, analysis of propensity score-matched pairs ($n = 217$) showed statistical significance in terms of increased risk of death in the thrombolysis arm *versus* no thrombolysis arm (OR 2.32; 95% CI, 1.15–4.68; $p = 0.018$) [Riera-Mestre *et al.* 2012].

Goldhaber and colleagues evaluated 2454 patients registered from the International Cooperative

Pulmonary Embolism Registry (ICOPER). Intracranial hemorrhage occurred in 3% of patients who received thrombolytic therapy *versus* 0.3% who did not. It was also estimated that the incidence of any major bleeding was 22% among the thrombolytic therapy group *versus* 9% in non-thrombolytic group [Goldhaber *et al.* 1999].

Weinberg and Jaff conducted a study to evaluate the role of thrombolysis in normotensive patients with sub massive PE and the effect on RV strain. All patients received low molecular weight heparin followed by randomization to either tenecteplase or placebo. The study, although terminated prematurely, revealed some interesting findings including three adverse events in the placebo arm and one fatal intracranial bleed in the tenecteplase arm. In conclusion, it was noted that 37% in the placebo arm and 15% in the tenecteplase arm had at least one adverse event ($p = 0.017$) [Weinberg and Jaff, 2013].

Gao and colleagues published a meta-analysis of 8 clinical randomized trials involving a total of 1755 patients with intermediate risk PE. Patients with thrombolytic therapy experienced a lower mortality rate than patients in the anticoagulation cohort [relative risk (RR), 0.52; 95% CI, 0.28–0.97; 1.39% (12/866) *versus* 2.92% (26/889)]. Compared with anticoagulation, thrombolytic therapy was associated with a higher risk of major bleeding (RR, 3.35; 95% CI, 2.77–4.84; 32.78% *versus* 8.94%). Furthermore, thrombolytic therapy was associated with a lower incidence of recurrent PE [RR, 0.33; 95% CI, 0.15–0.73; 0.73%; 0.73% (6/826) *versus* 2.72% (23/846)]. The authors concluded that, compared with anticoagulation thrombolytic therapy in patients with intermediate-risk PE, there is a lower all-cause mortality and recurrent PE risk despite increased major and minor bleeding [Gao *et al.* 2015].

Conclusions and future considerations

Novel approaches for the treatment over the past decade for massive and submassive PE have raised new clinical questions, both interesting and controversial, on the clinical utility, role, applicability of such therapeutic modalities and the specific criteria among investigators. Submassive PE is usually presented in normotensive patients with RV dysfunction and elevated biomarkers of myocardial injury/stress, which prompts clinicians for an early and adequate diagnosis, risk stratification for appropriate therapeutic decision making

Table 4. Predictors of major bleeding following thrombolysis in acute pulmonary embolism.

Characteristics
Male gender
Severe obesity
Hemodynamic instability
Current cancer
Metastatic cancer
Chemotherapy within 6 months
Hypertension
Diabetes mellitus
Creatinine >1.5mg/dl
Previous deep vein thrombosis or pulmonary embolism

during the short-term course of these patients. Research remains limited in terms of high quality data evaluating systemic thrombolysis in this clinical purview.

Our review focused on the main clinical trials addressing these issues with a particular emphasis on symptom improvement and evaluating hemorrhagic risk. In analysis of the forementioned trials in this review, we can note that all-cause mortality was similar in the 2 meta-analyses (2.17% in thrombolysis *versus* 3.89% nonthrombolysis therapy), although the risk of major bleeding was higher (9.24% *versus* 3.42%). When comparing the all-cause mortality or recurrent PE between the MAPPET-3, TIPES, MOPETT and PEITHO trials; the MAPPET-3 trial had the highest rate (3.4%) *versus* the TIPES trial, which had 1 death at 3 days and another at day 30 from MI, indicating the possibility of lower effectiveness of heparin plus alteplase therapy compared with tenecteplase plus heparin. Another interesting finding was different values of bleeding risk (intracranial or nonintracranial major bleeding) as Table 4 describes the major clinical predictors of bleedings post-thrombolysis. It was noted that PEITHO trial had the highest level of major non intracranial bleeding (6.3%) *versus* no bleeding at all in the MOPETT and MAPPET-3 trials. In short, IV tenecteplase had a better outcome in submassive PE treatment, although there was an increased risk of bleeding.

With regard to future trials, advancements will only continue to improve our current knowledge and standard treatment for submassive PE; clinical

studies and more consolidated data can provide additional information regarding that point.

Catheter-based, pharmacomechanical therapies have gained considerable interest lately. In particular, ultrasound-facilitated, catheter-directed thrombolysis has emerged as an attractive alternative therapeutic modality with an increasing number of single-center studies and ongoing randomized trials with promising preliminary results [Kucher *et al.* 2014; Piazza *et al.* 2015]. This is especially true among the subgroup of patients with very high risk of internal or intracranial bleeding and with absolute contraindications for systemic thrombolysis. Major trials are mentioned in the literature such as SEATTLE 2 and the use of EkoSonic system with promising results.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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