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Review of acute pulmonary embolism management and the evidence on intermediate-high risk PE

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Take Home Messages

- PE remains the third commonest cardiovascular disease in Europe, the severity of which is variable and can be lethal. The incidence is expected to increase due to the aging population.
- Risk assessment for early mortality should be undertaken if the patients are haemodynamically stable to guide management.
- Optimal treatment is still not established, especially for those that fall in the intermediate-high risk group.
- Thrombolysis remains a possible life saving treatment option for those of intermediate-high risk with evidence of deterioration. However aside from reducing the risk of acute PEA arrest, there are no proven long-term benefits of thrombolysis.
- For patients in who thrombolysis is contraindicated, on-going trials are taking place for interventional catheter mediated procedures which may provide more favourable risk profiles in the future.

Background and epidemiology

Pulmonary embolism (PE) is one form of venous thromboembolism (VTE) often secondary to deep vein thrombosis (DVT). It is the third most frequent cardiovascular disease in Europe with annual incidence rates between 100 and 200 per 100,000 (1, 2). VTE in general can be lethal in the acute phase or lead to chronic disease (3-6). Acute PE is more dangerous; however, the epidemiology is difficult to establish accurately due to cases often being asymptomatic or presenting with sudden death (2, 7). It is a major cause of mortality, morbidity and hospitalisation (2) and is expected to be an increasing problem in the future given the increasing proportion of the population living longer than ever before.
Registries and hospital datasets of unselected patients with VTE/PE show 30-day all-cause mortality rates between 9-11%, 3-month mortality between 8.6-17% (8-10). Following the acute episode, resolution of the thrombi is frequently incomplete, with some studies showing up to 35% of patients having abnormal perfusion scans up to a year post event (11-13).

Pathophysiology

Acute PE affects both the circulation and gas exchange however, right ventricular (RV) failure due to pressure overload is thought to be the main cause of death in severe acute PE. This will occur if more than 30-50% of the total cross-sectional area of the pulmonary arterial bed is occluded (14). Vasoconstriction mediated by the release of thromboxane A2 and serotonin contribute to the increase in pulmonary vascular resistance after acute PE,

which can be reversed by vasodilators (15-16). Both anatomical obstruction and vasoconstriction lead to increase in pulmonary vascular resistance and decrease in arterial compliance (17) which results in RV dilatation. This leads to increase in RV pressure and volume resulting in elevated wall tension and myocyte stretch and then right bundle branch block, which results in desynchronisation of the ventricles. Subsequent impairment of left ventricular (LV) filling in early diastole leads to a reduction in cardiac output and contributes to systemic hypotension and haemodynamic instability (18). Elevated levels of circulation biomarkers of myocardial injury are related to adverse outcomes due to RV ischaemia in the acute phase (19-21)

Acute RV failure with low cardiac output is the leading cause of death in high-risk PE, therefore supportive treatment is vital. Studies have shown that volume expansion is of no benefit but modest fluid challenges may help increase output in those with normal blood pressure (22-23). Vasopressors are often necessary in conjunction with, or prior to, reperfusion treatment. Respiratory failure in PE is primarily secondary to haemodynamic disturbances (24) due to low cardiac output and desaturation of mixed venous blood along with zones of reduced flow in obstructed vessels leading to ventilation-perfusion mismatch (25).

Diagnosis

Diagnosis involves a basic history and examination as well as the use of prediction/risk scores (WELL's), biochemical markers (d-dimer, troponin I or T) and imaging (computerised tomography pulmonary angiography (CTPA), ventilation-perfusion (VQ) scan, echocardiography). On confirming the diagnosis, the next step is to judge risk of mortality.

Prediction of early (30-day) outcomes in patients with acute PE should take into account both PE related risk as well as the patients' background medical history and clinical condition. However, in the presence of acute haemodynamic instability or overt shock, emergent diagnostic confirmation followed by primary reperfusion therapy is usually indicated.

In the absence of haemodynamic instability, once diagnosis of PE is confirmed, risk stratification should be performed to guide management. Commonly used scores for this purpose are the pulmonary embolism severity index (PESI) or simplified version (sPESI) to identify low vs intermediate risk. Around a third of PE patients are at low risk with PESI Class I or II, while those with PESI Class III-V have predicted 30-day mortality rates up to 24.5% (26-27). For those in the intermediate risk group, the assessment of the RV size and function as well as cardiac troponin levels help differentiate between intermediate high or intermediate low risk as they require monitoring for early detection of haemodynamic decompensation (28). Table 1 illustrates this early mortality risk assessment score and Table 2 summarises the PESI and sPESI scores as per European Society of Cardiology (ESC) guidelines (29).

Previous definitions of severity include massive and sub-massive PE. These are somewhat similar to PESI high risk and intermediate risk, but are based on volume of clot and how proximal it is in the arterial tree as well as evidence of RV dysfunction.

Early Mortality Risk	Shock or hypotension	PESI class III-V or sPESI ≥ 1	Signs of RV dysfunction on an imaging test	Cardiac laboratory biomarkers
High	+	+	+	+
Intermediate-high	-	+	+	+
Intermediate-low	-	+	+/- (one positive or neither)	+/- (one positive or neither)
Low	-	-	- (if tested)	- (if tested)

Table 1. Early mortality risk assessment of acute PE, adapted from (29), red highlights difficult treatment group/focus of discussion.

Parameter	Original version	Simplified version
Age	Age in years	1 point if age >80 years
Male sex	+10 points	-
Cancer	+30 points	1 point
Chronic heart failure	+10 points	1 point
Chronic pulmonary disease	+10 points	for either or both
Pulse rate ≥ 110 bpm	+20 points	1 point
Systolic blood pressure <100 mm Hg	+30 points	1 point
Respiratory rate >30 breaths per minute	+20 points	-
Temperature <36^0 C	+20 points	-
Altered mental status	+60 points	-
Arterial oxyhaemoglobin saturation <90%	+20 points	1 point
	Risk stratification	
	Class I: ≤ 65 points=very low 30-day mortality risk (0-1.6%) Class II: 66-85 points=low mortality risk (1.7-3.5%)	0 points= 30-day mortality risk 1.0%
	Class III: 86-105 points= moderate mortality risk (3.2-7.1%) Class IV: 106-125 points=high mortality risk (4.0-11.4%)	≥1 point(s)= 30-day mortality risk 10.9%
	Class V: >125 points=very high mortality risk (10-24.5%)	

Table 2. Original and simplified PESI scores and risk stratification, adapted from (29)

Management

Management of low or high-risk acute PE is relatively established and agreed upon however intermediate risk PE has been an on-going subject of discussion. Furthermore, the concern over bleeding risk with anticoagulation and therefore appropriate management for certain subgroups is also an area of concern.

Anticoagulation is the mainstay of treatment in acute PE with the aim of preventing death and recurrent VTE. Duration of anticoagulation should be at least 3 months but this may need to be adjusted depending on patient characteristics/history/underlying cause. Initial treatment is with one of unfractionated heparin, low molecular weight heparin (LMWH) or fondaparinux before switching to an oral anticoagulant such as warfarin or a direct oral anticoagulant (DOAC).

High risk patients with acute PE who are haemodynamically unstable can develop Pulseless Electrical Activity (PEA) circulatory arrest, therefore thrombolysis/primary reperfusion is advised in the absence of bleeding contra-indications (30) and is supported by all major guidelines. On the other end of the spectrum, low risk patients are usually best treated with anticoagulation utilising LMWH and oral agents and can often be treated as outpatients. No clear benefit of primary reperfusion has been shown in intermediate risk patients without haemodynamic instability, but multiple combinations of investigations have been tested to help guide risk stratification (31-37). For example, the combination of RV dysfunction on echocardiography or CTPA, with positive serum cardiac troponin (34, 38-39) was used in the PEITHO (pulmonary embolism thrombolysis) trial (28) which seems to be accurate and becoming more universally adopted, as appears in the guidelines.
Thrombolysis in patients without haemodynamic compromise has been an issue of debate and investigation for years. Previous data in a randomised comparison of heparin vs alteplase in normotensive acute PE patients with evidence of RV dysfunction or pulmonary hypertension showed that thrombolytic treatment (mainly secondary thrombolysis) reduced the incidence of escalation to emergency treatment from 24.6% to 10.2% without affecting mortality (40).

The more recent PEITHO trial was a multicentre, randomised, double-blind comparison of thrombolysis with a single weight adapted IV bolus of tenecteplase plus heparin vs placebo plus heparin. It enrolled 1006 patients (1005 actually took part) with mean age of 70 and acute PE with RV dysfunction confirmed on echocardiography or CTPA and myocardial injury confirmed on positive troponin I or T test. Specific average risk scores were not provided as there were variable percentages of medical comorbidities in the 2 groups which were balanced. However all patients required to fulfil criteria for intermediate-high risk acute PE. The study showed that death or hemodynamic decompensation occurred in 13 of 506 patients (2.6%) in the tenecteplase group as compared with 28 of 499 (5.6%) in the placebo group (odds ratio, 0.44; 95% confidence interval, 0.23 to 0.87; P=0.02) however this benefit was offset by higher rates of major bleeding (including fatal bleeding), and no reduction in 7-day or 30-day mortality in the tenecteplase group (28).

In another randomised study comparing LMWH vs LMHW+IV bolus of tenecteplase in intermediate risk PE, those treated with tenecteplase had fewer adverse outcomes and better functional capacity and quality of life at 3 months (41). Thrombolytic treatment obviously carries a major bleeding risk; analysis from pooled data from trials report intracranial bleeding rates between 1.9 and 2.2% (42-43).

Thrombolysis risks and alternative treatment options

In PEITHO there was a 2% incidence of haemorrhagic stroke after thrombolysis vs 0.2% for placebo in the intermediate-high risk group, primarily driven by outcomes in the over 75-year age group. Major non-intracranial bleeding events were also increased 6.3% vs 1.5% ($p<0.001$) in the placebo group (28). These results highlight the importance of identifying strategies to mitigate the risk of thrombolytic treatment. To this end, studies have shown improved safety with the use of reduced dose thrombolysis (44-45).

Surgical embolectomy for acute high-risk PE and for some selected patients with intermediate-high risk, where thrombolysis is contraindicated, has been performed successfully (46-47) down to the level of segmental pulmonary arteries. Pre-operative thrombolysis increases bleeding risk but is not an absolute contraindication (48). However, most hospitals do not have on site cardiothoracic surgery and are therefore not able to offer this option even for potentially suitable patients

Percutaneous catheter-directed treatments (usually reserved for patients with non-mobile, large size thrombi) aim to remove obstructing thrombi from the main pulmonary arteries to facilitate RV recovery, improve symptoms and survival (49). Even though most of the studies were not specifically designed for patients with contraindications to thrombolysis, the agreed advice is that for this population these procedures are safer. Catheter directed procedures include thrombus fragmentation with pigtail or balloon catheters/sonographic disruption, rheolytic thrombectomy with hydrodynamic catheter devices, suction thrombectomy with aspiration catheters and rotational thrombectomy. For patients without contraindication to thrombolysis, catheter directed thrombolysis is a preferred approach with or without combination of one of the above mechanical methods (49-50).

A review of such studies demonstrated improvement in haemodynamic parameters, resolution of hypoxia and survival to discharge up to 87% of patients (however 67% of those patients also received local thrombolysis in addition to mechanical catheter intervention). Risks of percutaneously delivered

therapy include death from worsening RV failure, distal embolization, pulmonary artery perforation and lung haemorrhage as well as systemic bleeding complications, cardiac tamponade, heart block, haemolysis and contrast induced nephropathy (49). Early RV recovery after low dose catheter directed thrombolysis appears comparable to that after standard dose systemic thrombolysis (51-52).

Catheter directed ultrasound accelerated thrombolysis reduced the sub-annular RV/LV dimension ratio significantly in the 24-hour follow up without increase in bleeding complications (53-55).

Conclusions

Thrombolysis has been shown to have positive outcomes from the point of view of reduction of symptoms, clots resolving faster compared to just anticoagulation as well as early reduction in pulmonary aortic pressure (PAP) and RV strain, decreased PE recurrence, and lower rates of early death or haemodynamic instability at 7 days as shown in PEITHO.

A follow up study of 709 patients from the PEITHO study showed that there were no long-term benefits/improvements in functional status or pulmonary hypertension, concluding that thrombolysis does not affect long-term morbidity in intermediate-high risk PE (56). Long term follow-up showed that there were no differences in mortality between the 2 groups (thrombolysis vs heparin alone) and a subgroup of 290 patients had long-term echocardiographic follow up which again showed no difference between the two groups with respect to estimated residual pulmonary hypertension or right ventricular dysfunction. Chronic thromboembolic pulmonary hypertension (CTEPH) development again was not different between the 2 groups (4 thrombolysis, 6 placebo). Furthermore, 36% of the thrombolysis group and 30% of the placebo group reported persistent symptoms, mostly mild exertional dyspnoea. Similar numbers (12% thrombolysis, 11% placebo) were classed as NYHA III or IV (56).

Therefore, thrombolysis mainly has evidence for use in high risk PE to avoid PEA arrest (30). In intermediate-high risk there is a theoretical advantage that thrombolysis could help in the event of further deterioration. One could argue that lower doses of thrombolytic agents or catheter-mediated thrombolysis may be the way forward in treating intermediate-high risk patients. With regards to bleeding risks, use of full-dose tenecteplase plus heparin IV bolus loading may have contributed to some degree to the high rates of bleeding seen in PEITHO. Some therefore advocate stopping heparin when thrombolysis is given.

Following the results of PEITHO we could conclude that if patients have signs of RV dysfunction on imaging and myocardial necrosis on serum biomarker testing, in combination with clinical signs of compromise, they are likely to benefit at least in the short term, from thrombolysis if they are under 75 years of age. Therefore, a reasonable approach may be to monitor these patients closely, assess contra-indications to thrombolysis and consider intervention if they deteriorate or fail to improve clinically. The short-term benefit needs to be balanced with the higher rates of bleeding and lack of long-term benefit in those surviving the acute phase. The optimal treatment strategy for intermediate risk PE patients therefore remains to be definitively established.

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