Thrombolysis for submassive pulmonary embolus

Reviewed and revised 23 July 2014

OVERVIEW

- thrombolysis is an established therapy for massive pulmonary embolism
- the use of thrombolytics for the treatment of submassive PE is controversial — the limited documented benefit (e.g. improved hemodynamics, potential for less chronic pulmonary hypertension) must be weighed against the increased risk of life-threatening hemorrhage
- definitions vary (see below), intermediate risk PE is sometimes used in preference to 'submassive'

DEFINITIONS

Background

- Massive PE was previously defined by anatomical criteria: >50% obstruction of pulmonary vasculature or occlusion of 2 or more lobar arteries
- It is now more commonly defined by hemodynamic instability, which is a function of both PE size and underlying cardiopulmonary status
- As such, a smaller PE in a patient with poor cardiopulmonary reserve could produce similar outcomes to a larger PE in a patient without prior cardiopulmonary disease

Massive PE (Jaff et al, 2011)

- Acute PE with:
  — sustained hypotension (SBP <90 mm Hg for at least 15 min or requiring inotropic support, not due to a cause other than PE, such as arrhythmia, hypovolemia, sepsis, or LV dysfunction)
  — pulselessness
  —or persistent profound bradycardia (heart rate <40 bpm with signs or symptoms of shock)

Submassive PE (Jaff et al, 2011)

- Acute PE without systemic hypotension (SBP ≥90 mm Hg) but with either RV dysfunction or myocardial necrosis

RV dysfunction means the presence of at least 1 of the following:

- RV dilation (apical 4-chamber RV diameter divided by LV diameter >0.9) or RV systolic dysfunction on echocardiography
- RV dilation (4-chamber RV diameter divided by LV diameter >0.9) on CT
- Elevation of BNP (>90 pg/mL)
- Elevation of N-terminal pro-BNP (>500 pg/mL); or
- Electrocardiographic changes (new complete or incomplete right bundle-branch block, anteroseptal ST elevation or depression, or anteroseptal T-wave inversion)

Myocardial necrosis:

- Elevation of troponin I (>0.4 ng/mL) or
- Elevation of troponin T (>0.1 ng/mL)

V dysfunction or a positive

igns and symptoms of PE
% involvement of thrombus
robability

ventilation/perfusion scan showing ventilation/perfusion mismatch in ≥2 lobes.

RATIONALE

- Rationale for thrombolytics
- thrombolytics do not completely clear the clot, but reduce the size
- an improvement in pulmonary resistance by about 10% can unload the RV

Mortality of submassive PE

- accounts for ~20% of all PE (numbers vary as we get better at detecting small PEs)
- 2-5% in-hospital death rate in RCTs of submassive PE
- Data from registries indicate that the short-term mortality rate directly attributable to submassive PE treated with heparin anticoagulation is probably < 3.0%
- a meta-analysis by Cho et al, 2014 found increased short-term mortality for hemodynamiclaly stable patients with RV dysfunction (OR 2.29; 13.7% vs 6.5% without RV dysfunction) (NB. there may be selection bias, as those patients that get an echo are more likely to be sick)
- hemodynamic instability may be 'masked' by normal systemic BP, Cho et al, 2014 found that of hemodynamically stable patients with PE, 37% have evidence of RV dysfunction on echo.

Morbidity of submassive PE

- The implication from the low mortality rate is that even if adjunctive fibrinolytic therapy has extremely high efficacy, for example, a 30% RR in mortality, the effect size on mortality due to submassive PE is probably < 1% then secondary adverse outcomes such as persistent RV dysfunction, chronic thromboembolic pulmonary hypertension, and impaired quality of life represent appropriate surrogate goals of treatment
- submassive PE accounts for most deaths from PE
- leads to longterm morbidity, especially chronic pulmonary hypertension and worse functional outcome
- In MAPPET-3, most cases of clinical deterioration occurred within the first five days

Predictors of poor outcome

- Odds ratio for short-term mortality for RV dysfunction on echocardiography = 2.53 (95% CI 1.17 to 5.50).
- Troponin elevations had an odds ratio for mortality of 5.90 (95% CI 2.68 to 12.95)

Low risk PEs are those with normal RV function and no elevations in biomarkers with short-term mortality rates approaching ≈ 1%

PROS

- Patients appear to fell better quicker
- Clots resolve faster (30% to 35% reduction in total perfusion defect at 24h, with minimal improvement if just anticoagulated) early reduction in PAP and RV strain
- Decreased recurrence of PE
- Decreased death or hemodynamic stability (composite endpoint) at 7 days (PEITHO trial)
- Improved functional outcome (unproven, TOPCOAT trial)
- less longterm pulmonary hypertension (MOPETT trial)

CONS

- risk of intracerebral haemorrhage (2% in >75y group in PEITHO)
- risk of other haemorrhage (major bleeding, i.e. transfusion needed, ~6% in PEITHO)
- similar improvement at 7 days overall ((≈65% to 70% reduction in total defect regardless of whether thrombolysed or anticoagulated)
- Increased cost
- No mortality benefit proven (improved composite of mortality and haemodynamic stability in PEITHO, as yet unpublished)

ADMINISTRATION OF THROMBOLYTICS

Thrombolytic selection, dose and route

- alteplase (patients 65 kg or more) 10 mg IV bolus, followed by 90 mg IV infusion over 2 hours (the MOPPET trial used half-dose, i.e. total of 50 mg)
- For patients weighing less than 65 kg, the total dose should be adjusted so that it does not exceed 1.5 mg/kg
- This total includes the 10 mg intravenous (IV) bolus dose and the following IV infusion (given over 2 hours)
- If alteplase is unavailable, consider use of streptokinase or tenecteplase as an alternative

- Once the initial haemostatic defect has partly resolved, with the APTT less than twice normal, use: unfractionated heparin 1000 units/hour IV infusion, adjusted with frequent APTT measurement to ensure therapeutic anticoagulation
- Tenecteplase (which has the advantage of bolus dosing) is not US FDA approved for acute PE, but other thrombolytic agents, including streptokinase, alteplase, and urokinase, are
- Use the peripheral IV route – no benefit to 'targeted' thrombolysis via CVC or PAC

Anticoagulation

- Anticoagulation with unfractionated heparin (UFH) via an infusion should be started, as the efficacy of low molecular weight heparins (LMWH) in this situation is unknown
- Use: unfractionated heparin 80 units/kg loading dose IV, followed by 18 units/kg/hour IV infusion, adjusted according to APTT
- In the acute stages of a major thromboembolic episode, there is often relative heparin resistance (up to 25% of VTE patients) and the dose requirement can be high. However, this heparin resistance can suddenly reverse, so APTT needs to be closely monitored (Factor Xa monitoring can also be used)
- Check APTT after 4-6 hours, then daily when stable

CONTRA-INDICATIONS TO THROMBOLYSIS

Absolute contraindications include

- any prior intracranial hemorrhage
- known structural intracranial cerebrovascular disease (eg, arteriovenous malformation)
- known malignant intracranial neoplasm
- ischemic stroke within 3 months
- suspected aortic dissection
- active bleeding or bleeding diathesis
- recent surgery encroaching on the spinal canal or brain, and
- recent significant closed-head or facial trauma with radiographic evidence of bony fracture or brain injury

Relative contraindications include

- age >75 years
- current use of anticoagulation
- pregnancy
- noncompressible vascular punctures

- traumatic or prolonged cardiopulmonary resuscitation (>10 minutes)
- recent internal bleeding (within 2 to 4 weeks)
- history of chronic, severe, and poorly controlled hypertension
- severe uncontrolled hypertension on presentation (systolic blood pressure >180 mm Hg or diastolic blood pressure >110 mm Hg)
- dementia
- remote (>3 months) ischemic stroke; and
- major surgery within 3 weeks

EVIDENCE

Chaterjee et al, 2014

- meta-analysis of 16 RCTs comparing thrombolysis with anticoagulant therapy in patients with PE
- n = 2115
- 4 trials accounted for 74% of the total patients
- NNT 59 for all cause mortality benefit, with mortality absolute risk reduction of 1.12%
- NNH 18 for major bleeding (not significant if <65 years of age)
- Study heterogeneity due to variations in definitions for haemodynamic instability, major and minor bleeding and RV dysfunction as well as varying doses and types of thrombolysis between studies
- One study used catheter directed thrombolysis (limited availabiliy), yet even with this study excluded the primary outcome was statistically significant
- MAPPETT-3 and PEITHO account for one-third of patients for this meta-analysis, and both have flows

Nakamura et al, 2014

- meta-analysis of 6 RCTs comparing thrombolysis with anticoagulant therapy in patients with PE
- n = 1510
- actually had a slightly larger absolute risk difference (1.6%) to Chatterjee et al, 2014, but due to a smaller sample size this was not significant
- similar to Chaterjee et al – a meta-analysis does nothing to replace a well designed RCT.

PEITHO trial, 2014

- DB MCRCT
- n = 1006 patients
- (mean age 70 years) in 13 countries in Europe and Israel,

- included patients with confirmed PE, an abnormal RV on echocardiography or CT, and a positive troponin I or T test result
- randomized to heparin plus placebo or heparin plus a weight-adapted bolus of tenecteplase
- combined primary end point was death from any cause or hemodynamic collapse after seven days
- primary end point RRR of 56% if treated with tenecteplase and heparin, compared with the heparin-only group (2.6% in the tenecteplase group vs 5.6% in the placebo group, p=0.015)
- substantial reduction in the combined endpoint of early mortality or hemodynamic collapse in patients receiving systemic thrombolysis (as compared to heparin alone)
- significant increase in major hemorrhage (including intracranial hemorrhage), particularly evident among elderly patients aged >75y
- major bleeding was significantly increased with tenecteplase: 6.3% vs 1.5% in the placebo group ($p<0.001$)
- subgroup analysis by age, in the >75y group RRR was 37% and the risk of stroke almost 2%
- commentary and criticisms:
    - tenecteplase group had higher rates of prior LMWH and/or fondaparinux use
    - use of composite endpoint
    - industry funding
    - lower dose thrombolysis may have less side-effects (see MOPPET trial)
    - does not assess morbidity for chronic pulmonary hypertension

MOPPET Trial, 2013

- open-label SC RCT, n= 121
- enrolled relatively ill PE patients – tachypneic, hypoxic, tachycardic patients with >70% thrombotic occlusion of lobar or main pulmonary arteries, RV dysfunction, elevated troponins, elevated BNP
- intervention group got 'half dose' thrombolysis: dosed tPA at 50mg, rather than 100mg – 10mg bolus and 40mg infusion
- long-term reduction in the incidence of pulmonary hypertension compared to anticoagulation alone (ARR 40% at 28 months, 57% vs 16% risk of pulmonary hypertension/ recurrent PE) without excess bleeding
- did not apply regularly applied measures of "submassive", used an anatomical definition based on clot extent
- commentary and criticisms:
    - open-label small study with a non-standard definition of 'moderate' PE, likely prone to bias

MAPPET-3 trial, 2002

- DB RCT

- n = 256 patients with acute pulmonary embolism and pulmonary hypertension or RV dysfunction but without arterial hypotension or shock
- heparin plus 100 mg of alteplase or heparin plus placebo over a period of two hours
- The primary end point was in-hospital death or clinical deterioration requiring an escalation of treatment, (defined as catecholamine infusion, secondary thrombolysis, endotracheal intubation, cardiopulmonary resuscitation, or emergency surgical embolectomy or thrombus fragmentation by catheter)
- no difference was shown for in-hospital mortality (3.4% versus 2.2%; P=0.71)
- more cases of clinical deterioration requiring therapy escalation in the group of patients treated with heparin alone (24.6 versus 10.2%; P=0.004)
- Only 31% of patients had Echo confirmed RV strain
- no significant difference in the incidence of major bleeding between the two groups

RIETE, 2006

- retrospective cohort study of 15,944 patients with an objectively confirmed symptomatic acute PE, identified from the multicenter, international, prospective, Registro Informatizado de la Enfermedad TromboEmbólica (RIETE registry)
- In the normotensive subgroup, analysis of propensity score-matched pairs (n = 217 pairs) showed a statistically significant and clinically meaningful increased risk of death for thrombolysis compared with no thrombolysis (OR 2.32; 95% CI, 1.15-4.68; P = 0.018)

ICOPER registry, 1999

- intracranial bleeding occurred in 3% of patients who received thrombolytics versus 0.3% of those who did not
- The incidence of any major bleeding was 22% versus 9% in these groups (Goldhaber 1999).

Problems with studies

- inconsistent definitions of submassive PE, e.g. RV strain or elevated BNP are likely to be more important than just pulmonary hypertension or new RBBB on an ECG, or other anatomical definitions
- lack of functional outcomes
- probably practice misalignment due to lack of stratification of risk within the the submassive PE group
- Echocardiography is insensitive in distinguishing acute RV dysfunction from pre-existing changes

CONCLUSION

Overview

- The clinician is in the best position to judge the relative merits of fibrinolysis on a case-by-case basis
- For submassive PE thrombolysis the underlying diagnosis and stratification of risk should be carefully assessed
- assess for RV dysfunction (ECHO, BNP) and myocardial necrosis (Trop), if both are present or the patient 'looks sick' the patient will probably benefit from thrombolysis (at least if <75 years of age), but we cannot be certain
- Future studies need to further assess risk stratification, functional outcomes and dosing of thrombolytics

An approach

- monitor patients with RV dysfunction closely
- ensure there are no contra-indications to thrombolysis
- if the patient does not improve over the first few hours (e.g. 4 hours) or deteriorates then consider thrombolysis
- consider using 'half-dose' thrombolysis and monitor effect (e.g. improvement in RV function on Echo)
- thrombolysis can be performed as late as 14 days after the onset of the first symptoms

References and Links

Journal articles

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FOAM and web resources

- EMCrit — Podcast # 51: Fibrinolysis in Pulmonary Embolism (2012)
- EMCrit — Podcast 128 – Pulmonary Embolism Treatment Options and the PEAC Team with Oren Friedman (2014)
- EMCrit Wee — MOPETT trial (2013)
- EMLON — MOPETT – Half-Dose tPA for PE (2013)
- EMLON — Dueling PE meta-analyses (2014)
- EMNerd — The Adventure of the Greek Interpreter Revisited (2014)
- Medscape — PEITHO: Persuasive for Thrombolysis in PE? (2013) [PDF of PEITHO trial ACC presention slides]
- Medscape — The case for thrombolysis in PE: PEITHO, ULTIMA, and TOPCOAT with Dr Stavros Konstantinides (2013)
- Medscape — ULTrasound Accelerated ThrombolysIs of PulMonAry Embolism (ULTIMA), Tenecteplase or Placebo: Cardiopulmonary Outcomes At Three Months (TOPCOAT) (2013)
- Medscape — MOPETT: Is half-dose thrombolysis feasible for moderate PE? (2013)
- Medscape — Ultrasound plus fibrinolysis reduce right heart dysfunction in pulmonary-embolism patients (2013)
- PulmCCM — Thrombolytics (tPA) improve

intermediate risk PE outcomes, with a few head bleeds (PEITHO Trial) (2014)

- PulmCCM — Thrombolytics for acute pulmonary embolism (ACCP Guidelines) (2012)
- Resus.ME — Thrombolysis in submassive PE – still equipoise? (2011)

About Chris Nickson

An **oslerphile** emergency physician and intensivist suffering from a bad case of knowledge **dipsosis**. Key areas of interest include: the ED-ICU interface, toxicology, simulation and the free open-access meducation (FOAM) revolution. @**Twitter** | **+ Chris Nickson** | **RAGE** | **SMACC** | **iTeachEM**

Comments

Marc says

April 19, 2014 at 12:03 am

Love this -- Thanks for having all this great information available in a single location

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Werner JVR says

May 3, 2014 at 6:23 am

Thank you to all you guys for doing such an amazing job … LITFL rocks !

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