September 2014

Washington University Emergency Medicine Journal Club
Thrombolytics for Submassive Pulmonary Embolism

Vignette

You are working a day shift in your ED when you meet a generally healthy 55 year old male who acutely developed chest pain and shortness of breath at home. He tells you that he underwent an orthopedic procedure 10 days prior. He is tachycardic and has an oxygen saturation of 94% on room air. You order an EKG, which demonstrates an S1Q3T3 pattern and a troponin level which is very mildly elevated at 0.12. You think to yourself, "I've got this diagnosis" and order a PE protocol CT which identifies bilateral acute pulmonary emboli with a significant clot burden as well as dilation of the right ventricle. A bedside cardiac ultrasound was suggestive of right ventricular dilatation, so you send the patient to the Cardiac Diagnostic Lab for a formal ECHO, which reveals a markedly dilated right ventricle with flattened septal motion, McConnell's sign of right ventricle apical hyperkinesis, and tricuspid regurgitation consistent with right ventricular dysfunction in the context of an acute pulmonary embolism.

Given the relatively young age of the patient and his previously normal cardiac function, you consider whether to offer thrombolytic therapy given the degree of right ventricular dysfunction seen on ECHO. However, the patient has a SBP > 110 and is on room-air, and hence does not meet criteria for a "massive" PE. You wonder whether there is any recent data that can help you decide whether to offer thrombolysis in more "submassive" PE. You ask yourself "what can I tell my patient about the effect on his overall risk of mortality and long term functional outcome?"

You begin by reading a previous Washington University Journal Club on this topic from July 2010, at which time the evidence was sparse, and a firm conclusion could not be drawn. You decide to see if any new literature exists, formulate your PICO question, and start your search. Luckily for you, there have been a lot of recently published articles attempting to answer your very question.

PICO Question
Population: Adult patients with pulmonary embolism and evidence of right heart strain, with stable hemodynamics.
Intervention: Thrombolytic therapy.
Comparison: Anticoagulation with heparin, low molecular weight heparin (LMWH), or novel anticoagulants.
Outcome: Death, hemodynamic collapse, need for intubation, long-term functional outcomes, and quality of life.

Search Strategy

In addition to the recently published PEITHO study, a PubMed search was performed using the strategy: ((“Thrombolytic Therapy"[Mesh] OR "Fibrinolytic

Agents"[Mesh]) AND "Pulmonary Embolism"[Mesh]) with filters for meta-analysis, randomized controlled trial, and limited to the last 5 years (http://tinyurl.com/omwebmt). This resulted in 22 articles, from which 2 RCTs and a meta-analysis were chosen.

Article 1: Sharifi M, Bay C, Skrocki L, Rahimi F, Mehdipour M; "MOPETT" Investigators. Moderate pulmonary embolism treated with thrombolysis (from the "MOPETT" Trial). Am J Cardiol. 2013 Jan 15;111(2):273-7. Answer Key.

Article 2: Kline JA1, Nordenholz KE, Courtney DM, Kabrhel C, Jones AE, Rondina MT, Diercks DB, Klinger JR, Hernandez J. Treatment of submassive pulmonary embolism with tenecteplase or placebo: cardiopulmonary outcomes at 3 months: multicenter double-blind, placebo-controlled randomized trial. J Thromb Haemost. 2014 Apr; 12(4):459-68. Answer Key.

Article 3: Chatterjee S, Chakraborty A, Weinberg I, Kadakia M, Wilensky RL, Sardar P, Kumbhani DJ, Mukherjee D, Jaff MR, Giri J. Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis. JAMA. 2014 Jun 18;311(23):2414-21. Answer Key.

Article 4: Meyer G, Vicaut E, Danays T, Agnelli G, Becattini C, Beyer-Westendorf J, Bluhmki E, Bouvaist H, Brenner B, Couturaud F, Dellas C, Empen K, Franca A, Galiè N, Geibel A, Goldhaber SZ, Jimenez D, Kozak M, Kupatt C, Kucher N, Lang IM, Lankeit M, Meneveau N, Pacouret G, Palazzini M, Petris A, Pruszczyk P, Rugolotto M, Salvi A, Schellong S, Sebbane M, Sobkowicz B, Stefanovic BS, Thiele H, Torbicki A, Verschuren F, Konstantinides SV; PEITHO Investigators. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med. 2014 Apr 10;370(15): 1402-11. Answer Key.

Bottom Line

Venous thromboembolic disease, including both deep venous thrombosis (DVT) and pulmonary embolism (PE), is a prevalent condition, affecting an estimated 300,000 to 600,000 individuals in the US each year (Beckman 2010). Pulmonary embolism alone affects approximately 23 individuals per 100,000 (Anderson 1991). Given the high mortality of nearly 50% (Kucher 2006) in patients with PE and hemodynamic instability - i.e. "massive" PE - guidelines universally recommend considering the use of systemic thrombolytics in such cases (AHA, ESC, ACEP, NICE).

The use of thrombolytic therapy in hemodynamically stable patients with signs of right ventricular (RV) dysfunction - i.e. "submassive" PE - is highly debated. The guidelines vary widely in the their recommendations, from firmly stating "Do not offer pharmacological systemic thrombolytic therapy to patients with PE and haemodynamic stability" (NICE), to noting that there is insufficient evidence to make recommendations (ACEP), to clearly recommending thrombolysis when there is evidence of RV dysfunction or elevated cardiac biomarkers (AHA). In the last year, at least 2 randomized controlled trials evaluating thrombolysis in submassive PE have been published, along with a recent meta-analysis, which dwarf much of the data

previously published. As a result, it will be important to review this new data and update existing guidelines accordingly.

While mortality rates in hemodynamically stable patients with PE are much lower than in those with massive PE, ranging from 3% to 15%, the presence of RV dysfunction on ECHO confers nearly double the risk of death (unadjusted risk ratio 2.4), while elevations in cardiac biomarkers confer an even greater increased risk (Sanchez 2008). In addition to potential mortality benefit from thrombolysis, some have theorized a potential to decrease the long-term morbidity associated with large clot burden. The incidence of symptomatic chronic thromboembolic pulmonary hypertension (CTEPH) following venous thromboembolic disease is low, at around 4% at 2 years (Pengo 2004). There is no conclusive evidence that large clot burden, RV dysfunction, or elevated cardiac biomarkers increase this incidence. Prior observational studies have suggested that this incidence is reduced by the use of thrombolytics (Kline 2009), but no randomized trials have supported this finding conclusively.

A prior journal club on this topic conducted in 2010 was limited by the lack of randomized trials assessing patient-important outcomes. We therefore sought to update our findings in light of the recent influx of higher quality evidence in this area. The MOPETT trial evaluated the use of low-dose tPA in those with "moderate" PE, here defined as PE involving 2 or more lobar or main pulmonary arteries. A significant decrease in the incidence pulmonary hypertension was observed (number needed to treat [NNT] 2.4) with no difference in mortality or recurrent PE. Oddly, there were no bleeding events reported in either group. The primary outcome here was unfortunately based on ECHO findings, and does not necessarily translate into patient-important outcomes. In contrast to MOPETT, the TOPCOAT study sought to evaluate functional capacity and quality of life following the use of tenecteplase in patients with PE and either RV dysfunction or elevated cardiac biomarkers. The authors found a reduction in a composite outcome of "adverse events" defined as recurrent PE or DVT, death, poor functional capacity, or poor quality of life (NNT 4.5). However, the groups had similar mortality rates, and it is unclear from the study whether the driving factor for these results was a decrease in patient-important outcomes (quality of life), or surrogate outcomes (ECHO findings). This fact, along with the unfortunate note that the study was stopped early, makes interpretation of these results difficult.

The largest study on this topic to date (PEITHO) was a double-blind study in which patients with both RV dysfunction and an elevated troponin were randomized to either anticoagulation alone, or anticoagulation plus a bolus of tenecteplase. They reported a significant decrease in the combined risk of death or hemodynamic decompensation at 7 days (NNT = 33), but a significant increase in the risk of major bleeding (NNH = 14). Mortality itself was similar in the two groups, and the benefit seen in the primary outcome was derived largely from a decreased risk of hemodynamic decompensation. Given the high risk of bleeding found, particularly intracranial bleeding, it would be important to know the functional outcomes of survivors. It is difficult to fully assess the trade-off in this study between benefit

(decreased risk of hemodynamic decompensation) and harm (increased risk of major bleeding).

Finally, a recent meta-analysis (Chatterjee 2014) demonstrated an improvement in mortality, with a NNT of 59 for thrombolysis in all patients with PE, regardless of severity. This mortality benefit was balanced by an increased risk of major bleeding, with a NNH of 18. Specifically, for patients with "intermediate-risk" PE, the mortality benefit was slightly smaller (NNT 65) while the risk of major bleeding was the same (NNH 18). The degree of heterogeneity in the included studies, including poorly defined criteria for "intermediate-risk," poorly defined criteria for "major bleeding," and differing routes of administration of thrombolytics, limit our ability to draw firm conclusions from the meta-analysis. For example, the ULTIMA study was included in both meta-analyses, and involved ultrasound-assisted catheter-directed administration of thrombolytics. One could argue that pooling results from such disparate studies make little clinical sense, and one should interpret these results cautiously (if at all).

Despite an influx of new evidence over the last few years, the debate over thrombolysis in "submassive" or "intermediate-risk" PE rages on. Recent studies have failed to show a mortality benefit, whether measured 5 days (TOPCOAT), 7 days (PEITHO), or months (MOPETT trial) after administration, and a trade-off between hemodynamic decompensation and bleeding predominates. Some have proposed longterm functional benefits in those with significant clot burden or evidence of RV strain, but high-quality studies have yet to demonstrate an improvement in patient-important functional outcomes. While MOPPET demonstrated improved pulmonary artery systolic pressures on ECHO, the relationship between such a finding and patient-centric outcomes is unclear at best. The TOPCOAT study demonstrated an improvement in a composite outcome including death, recurrent DVT or PE, ECHO findings, functional capacity, and quality of life, but the contribution from each individual component is unclear, and it is difficult to translate these findings into clinical practice. For now, thrombolysis should be reserved for those with hemodynamic decompensation, or those felt to be at high risk of decompensation whose bleeding risk does not outstrip the potential benefit.