Thrombolytic therapy for submassive pulmonary embolus? PRO viewpoint

Luke S Howard

If we had robust evidence one way or the other to inform us on the use of thrombolytics in submassive pulmonary embolus (PE), we would not need this debate. But, we do not and, so, we do. The stakes are considered high both in favour and against thromobolysing submassive PE, so we cannot brush the debate under the carpet while we await the evidence. It is accepted that high-risk/massive PE, defined as haemodynamic instability, merits aggressive treatment due to unacceptable mortality, which outweighs the risk of haemorrhage. At the other end of the spectrum, patients with low-risk PE do not, such that they may even be treated as outpatients.

This leaves a grey area in between. When faced with a patient with a large thrombus load with a right ventricle (RV) that is dilated and pressure-loaded, but who is normotensive, as the attending clinician, we know they are at increased risk of death and long-term complications, such as chronic thromboembolic pulmonary hypertension (CTEPH).[1 2] We may fall back on the Hippocratic Oath to '*first, do no harm*', but the fuller translation reads '*I will use treatments for the benefit of the ill in accordance with my ability and my judgment, but from what is to their harm and injustice I will keep them*'. Thus, rather than hide behind a lack of evidence, we must review what we have and come to a balanced decision, and justify it.

In proposing the argument that submassive PE should be treated with thrombolysis, we must first accept that direct mortality due to the PE itself, not confounding conditions, remains unacceptably high with anticoagulation alone. A more aggressive strategy is required. As long as the benefits of thrombolysis outweigh the risks, then thrombolysis offers the best currently available approach. When this is coupled with the further benefits of likely reduction in CTEPH, the case becomes even stronger.

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The American Heart Association (AHA)[3] has proposed a definition of submassive PE as either:

- RV dysfunction, defined as RV dilation on echocardiography or CT, systolic dysfunction on echocardiography, elevation of brain natiuretic peptide (BNP)/N-terminal pro BNP (NT-proBNP) or evidence of new RV strain on ECG; or
- myocardial necrosis, defined as elevation of troponin I or T.

These measures either alone or in combination have been shown in many studies to be associated with worse survival, but this definition itself has not been prospectively studied. Jimenez *et al*[4] collected data from 591 normotensive PE patients (those who had received thrombolysis at the physician's discretion were not included) and showed that there was a 10% overall mortality. Pulmonary embolism may often occur on the background of other serious medical conditions, which may themselves lead to death. In these cases, it is hard to see how thrombolysis could improve the outcome, but Jimenez *et al* demonstrated that the rate of PE death, as opposed to all cause death, was 6.7%. When some of the criteria for submassive PE were applied, the rate of PE-related mortality increased to 11% with a positive troponin, 12% with echocardiographic evidence of RV dysfunction and 10% with complete compression ultrasound evidence of deep vein thrombosis (DVT).

Presented with data such as these, we may ask why studies of thrombolysis have not shown improvement in mortality. The reasons may be twofold. The first is that patients recruited into studies may have less severe disease, either due to a looser definition of submassive PE or due to those with more severe signs of right heart dysfunction not being recruited at the physician's discretion in order they be thrombolysed outside the protocol. Looking at the largest trial to date of thrombolysis in submassive PE,[5] only 31% of patients in the standard treatment arm had RV dysfunction on echocardiography and the mortality rate in that same arm was just over 2%. Contrast this with >10% mortality in the study by Jimenez *et al*[4] if patients had one or more of RV dysfunction, positive troponin or DVT. The AHA document[3] pools all the randomised thrombolysis studies in PE up to 2011, and only one has more than 100 patients in each arm[5] and it is therefore also not surprising to appreciate that these studies will be underpowered to detect a significant reduction in mortality. The studies were performed in different categories of patients and over 40 years, making pooling difficult, although it is worth noting there was a 30% non-significant reduction in mortality in the patients receiving thrombolysis. We can perhaps therefore conclude that trials may be under-representative of the true mortality of submassive PE. Of interest, however, a study not included, due to later publication,[6] randomised only patients with documented RV dysfunction on echocardiography, thus enriching the population, and in this study there was a significant reduction in PE-related mortality with 6/35 patients dying in the heparin group and 0/37 dying in the thrombolysis group.

The second reason that trials so far may not have shown a reduction in mortality is that they allow for thrombolysis in the event of haemodynamic collapse. To capture this effect, studies often combine mortality with haemodynamic collapse to detect a treatment response.[5 7]

The authors of the AHA document suggest that since the mortality seen in trials for submassive PE is less than 3%, even with highly effective therapy reducing mortality by 30%, trials will be unsuccessful in proving a mortality benefit, and thus surrogate endpoints should be used.[3] Since we know that PE-related mortality is linked to RV dysfunction which in turn is largely caused by clot burden[2] (likely to be a combination of burden in the lung and leg veins, since DVT increases the risk of death[4]), two good possible surrogates for mortality are haemodynamics and clot resolution.

A recent randomised study of thrombolysis in 'moderate' pulmonary embolism measured systolic pulmonary artery pressure (sPAP) as estimated on echocardiography as its primary endpoint. Thrombolysis versus anticoagulation resulted in a significantly lower sPAP at 48 h. Showing this fall in sPAP at such an early time point is critical to its credibility as a surrogate for PE-related mortality. This has also been documented in several other studies.[3] If only patients with RV dysfunction are considered, thrombolysis improves early RV function and BNP compared with placebo.[6]

The rate of clot resolution over the first 24 h has been shown to change very little with heparin, whereas with thrombolysis,

there is a 30%–35% reduction in perfusion defect.[3] For patients with RV dysfunction, it is this early resolution of clot with thrombolysis which will prove to be beneficial in reducing early complications. One may also postulate that earlier resolution of DVT with thrombolysis may also improve outcomes, since further embolisation may be fatal. Of note, the study by Fasullo *et al*[6] showed a trend towards better DVT resolution in patients receiving thrombolysis, only just missing statistical significance. It will take a large and well-constructed trial with mortality comparable with real-life data in the placebo arm to show mortality benefit with thrombolysis; until that time, surrogate data strongly suggest thrombolysis directly reduces the risk factors for death.

In addition to early PE-related mortality, there are important long-term outcomes from PE, in particular CTEPH. While it may not be common in all comers with PE, 2%–4% of cases,[1] it is likely to be much more common in those patients who have had submassive PE. No study has been performed rigorously using right heart catheterisation to study the incidence of CTEPH postsubmassive PE, especially given the variation in definition. Nonetheless, despite its likely low incidence, in itself it carries a significant risk of death.[1] Even if amenable to surgical endarterectomy, this is a very major surgical operation with its own mortality (<5%) and morbidity.[8] The argument may be less persuasive than early mortality since the associations are less direct, but adds to the weight of the argument in favour of thrombolysis.

Many studies referenced in the AHA statement,[3] in particular those by Kline *et al*[9] and Fasullo *et al*,[6] show lower long-term pulmonary arterial pressures and better RV function in those who were treated upfront with thrombolysis. How much of the improvement in RV function relates to more rapid relief of RV afterload cannot be certain, but the lower pulmonary pressures would suggest better clot resolution, which in itself is associated with lower 6-month mortality.[10] Why anticoagulation fails to catch up with thrombolysis is not fully understood, but studies of plasmin-mediated cleavage of fibrin have demonstrated resistance to fibrinolysis in patients with CTEPH compared with those with acute PE.[11] Allowing endogenous clot lysis to take place 'passively' using heparin alone may not be sufficient therefore to prevent progression to CTEPH in some patients. Identifying these patients upfront is not currently possible, but those with acute pulmonary hypertension are at the greatest risk of CTEPH.[1] That many patients presenting with CTEPH have in the past received thrombolysis[12] is not relevant, since many of these patients will have suffered previously unresolved PE.

While there can be little doubt that thrombolysis leads to faster and possibly more complete clot resolution, it is the risk of serious bleeding, in particular intracranial haemorrhage, which causes reticence when considering thrombolysis. This is a real concern and should not be taken lightly, but what we must consider is the balance of benefit against risk. A recent very large registry study of nearly 16 000 patients with PE showed a non-significant trend towards increased bleeding-related mortality at 90 days in those who received thrombolytics.[13] While the mortality was nearly double in the thrombolysis group (1.16% vs 0.61%, p=0.16), in absolute terms the rate was very low. Given that the entire cardiac output transits through the lung, it has been argued that lower doses of thrombolytics could be used with equal efficacy. Two recent studies have done just this,[14 15] showing equivalent clot resolution and lower rates of bleeding, although the numbers remain small in comparison with large registry studies.

It is the intention of the PEITHO investigators that this debate is settled once and for all,[7] but for the reasons explained above, namely, lower overall than expected mortality and the use of rescue thrombolysis, the PE-related mortality signal may be watered down. Until the data provide a clear answer, we must use our judgement.

In summary, outcomes in patients with true submassive PE remain unacceptably high and thrombolysis has been shown to improve surrogate outcomes for mortality as well as long-term complications. The risks from thrombolysis are low, and when reduced doses are used, evidence so far suggests no decrease in benefit, but a further reduction in bleeding. The next patient you see with submassive PE will want you to act on your best judgement rather than hide behind a 'lack of evidence'.

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Thrombolysis for acute submassive pulmonary embolism: CON viewpoint

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The normotensive patient with confirmed pulmonary embolism (PE) and right ventricular (RV) dilatation presents a significant dilemma to clinicians. On one hand, a string of publications have demonstrated that RV dysfunction is associated with adverse outcomes in patients with PE;[1–5] on the other, thrombolysis carries a significant risk of bleeding.[6 7] However, evidence emerging in recent years has provided a strong case against using thrombolysis in this setting, greatly aiding clinical decision-making in submassive PE (taken here to mean confirmed PE in a normotensive patient with evidence of RV dilatation and/or RV dysfunction and/or pulmonary hypertension). The aim of this article is to review some of the most important data surrounding this debate.

The decision to administer systemic thrombolysis would be easier if submassive PE had a high mortality rate that was significantly reduced by treatment. However, this is not the case. In larger studies, inhospital or 30-day mortality for submassive PE treated without thrombolysis is typically between 1% and 5%,[3 8–11] though lower and higher rates have been described.[12–14] In the excellent, landmark randomised controlled trial (RCT) of thrombolysis versus heparin alone for submassive PE, mortality was 3.4% in the thrombolysed group and 2.2% in the 'heparin-alone' group.[8] The argument is commonly made that trials exclude elderly patients or patients with comorbidities, artificially reducing mortality rates. However, the large RIETE registry also suggests a 90-day mortality of around 3% in patients with submassive PE.[15] The problem for advocates of thrombolysis in PE is that it may be technically impossible to demonstrate beneficial effects on mortality. This is because an RCT comparing thrombolysis and standard treatment would require prohibitively large numbers of patients to generate sufficient statistical power to detect a clinically meaningful difference in mortality.

Faced with this problem, those who champion thrombolysis might argue first that RV dilatation (and particularly persistent RV dilatation)[16] is associated with a poor prognosis in PE,[1–5] and second that thrombolysis improves RV dynamics acutely.[17–20] Consequently, they may suggest we should thrombolyse patients who have sufficient thrombus load to generate RV dilatation. Again, however, there is very little evidence in submassive PE to support this contention. A crucial point is that RV dilatation is a dynamic process. A large study indicated that 93% of patients with submassive PE, treated without thrombolysis, had normal RV systolic pressure (assessed by echocardiography) 6 months after diagnosis.[10] The same study reported two inpatient deaths among 200 patients with submassive PE.[10]

The emerging picture is that, at the point of presentation, patients with submassive PE are highly likely to survive if treated with heparin alone and that the associated RV dilatation is likely to resolve spontaneously in the significant majority. The nagging doubt, of course, surrounds the small proportion of patients who will have persistent RV dysfunction, particularly as this group seems vulnerable to recurrent venous thromboembolism (VTE).[16] The decision to give thrombolysis would again be easier if, at the point of presentation, we had tools accurately identifying those patients in whom RV function will fail to improve. However, two problems arise. First, while biomarkers such as brain natriuretic peptide afford some additional information,[21–24] they do not yet provide anywhere near the level of prognostic accuracy on which to base the decision to thrombolyse.[25] Second, even if they did, we have no evidence to suggest that early thrombolysis could outperform existing treatment options for these patients. Extending this argument, the two major concerns in patients with persistent RV dysfunction are the higher rate of recurrent VTE in patients with residual thrombus load[16 26] and the development of chronic thromboembolic pulmonary hypertension (CTEPH).[27 28] However attractive it may be theoretically, we have no strong evidence to inform whether early thrombolysis can reduce VTE recurrence—we know that longer-term anticoagulation does.[29] Similarly, we have no evidence that early thrombolysis reduces the risk of CTEPH, yet modern treatments significantly improve outcomes for this important complication.[30 31] So, instead of early thrombolysis, why not repeat echocardiography at 3 months, prolong anticoagulation in those with persistent RV impairment and assess carefully for evidence of CTEPH in the ensuing period?

The theoretical argument against this approach might be the hypothesis that thrombolysis improves haemodynamics acutely and that a normally functioning RV might lead to fewer complications downstream. However, careful studies have shown that while thrombolysis improves RV dilatation more than heparin alone in the first 12 h, the benefits are lost by 48 h.[20] There is no evidence in submassive PE to suggest that the early haemodynamic improvements translate into benefits in terms of survival, VTE recurrence or development of CTEPH.[8] Where early thrombolysis does seem to benefit patients with submassive PE is in reducing the amount of supportive care (eg, blood pressure support) required in the early stages of admission to hospital.[8] However, again, at the point of presentation, we have no accurate way to predict which patients will require extra haemodynamic support, and the extra supportive care we can give obviates any excess mortality in patients who do not receive thrombolysis.

The arguments against thrombolysis above would matter less if the risks of bleeding associated with thrombolysis were acceptable. Registry data and data from existing RCTs suggest that in the specific setting of PE, thrombolysis is associated with major bleeding rates of

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10%–20%.[6 7 32 33] The great anxiety with thrombolysis clearly relates to major intracranial haemorrhage (ICH). The large ICOPER registry reported that 3% of patients receiving thrombolysis for PE developed ICH;[6] other studies report rates approximating to this value.[34] We must keep in mind that 30-day mortality in submassive PE (with or without thrombolysis) is around 3%. Data suggest that the risk of haemorrhage after thrombolysis for PE is greater in older patients and patients with cancer,[7] precisely the groups known to be at the highest risk of death from PE.[15] Other interesting evidence suggests that women may be at higher risk for thrombolysis-induced haemorrhage than men, while simultaneously having lesser haemodynamic benefits,[33] but this requires confirmation.

The arguments presented above are firmly against routine use of thrombolysis in submassive PE. They are in keeping with the conclusions of recent comprehensive international guidelines and meta-analyses which found no evidence to support thrombolysis in this setting.[35–37] However, in many ways the real question should be whether, as a profession, we improve outcomes for patients when we give thrombolysis in the 'real world'. Perhaps clinical experience and assessment at the bedside drive a beneficial use of thrombolysis that could be undetectable in trials or in strict study protocols? Two recent studies throw light on this issue. Data from the large RIETE registry suggest that we do use thrombolysis to advantage in hypotensive patients with PE.[38] However, interestingly, thrombolysis was associated with significantly increased mortality (odds ratio 2.32) among normotensive patients with symptomatic acute PE.[38] A further study from Pennsylvania provided additional interesting insights—not only did surprisingly few patients with PE receive thrombolysis, but mortality from thrombolysis was significantly increased among patients in whom indications for the treatment were the lowest.[39] While recognising inherent limitations in retrospective studies, and the fact that the latter study did not specifically analyse submassive PE, the inference seems to be that doctors appear reluctant (perhaps nervous) to give thrombolysis for PE and that inappropriate thrombolysis has important detrimental consequences.

We are left in a difficult and sobering position when faced with a patient with submassive PE. The evidence would suggest that your patient has around a 2%–3% chance of dying in hospital and you are highly unlikely to save his/her life in the acute phase by using thrombolysis. The RV dilatation is highly likely to resolve spontaneously. There is a chance of up to one in five that you will induce significant bleeding with thrombolysis, and a one in 30 chance that you will cause ICH. Results from the important, large and beautifully designed PEITHO trial of thrombolysis for normotensive patients with RV dysfunction have been eagerly awaited in the expectation that they will provide increased clarity in this debate.[40]

The literature currently cannot help with your anxieties that a very small proportion of patients with submassive PE will progress to recurrent VTE or CTEPH, and that at the point of presentation you cannot accurately predict who they will be. However, you at least know that you can monitor patients with submassive PE and that you have effective, proven therapeutic options for preventing recurrent PE and treating CTEPH.

The real problem of course (and part of the reason for having this important debate) is that we have no reliable and accurate tools to pinpoint the important minority of patients with submassive PE who genuinely might benefit from thrombolysis or perhaps from surgical embolectomy. Biomarkers and risk profiling are slowly leading us in the direction of this kind of stratified medicine, and this is a key area for future research. A further, very exciting prospect (as highlighted in the accompanying article (http://dx.doi.org/10.1136/thoraxjnl-2013-203413)) is whether low dose thrombolysis can impact on clinically important endpoints in submassive PE without the unacceptable risks of haemorrhage. The recent MOPETT trial offers some real hope in this regard, but will face the exceptionally difficult trial design issues inherent to demonstrating benefits in meaningful clinical endpoints.[41] In the meantime, the real risks of causing unintentional harm to our patients cast a forbidding shadow over the theoretical benefits of thrombolysis in submassive PE.

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