Thrombolysis for acute submassive pulmonary embolism: CON viewpoint

A John Simpson

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

Correspondence to Professor John Simpson, Institute of Cellular Medicine, 4th Floor, William Leech Building, Medical School, Newcastle University, Newcastle upon Tyne NE2 4HH, UK; j.simpson@ncl.ac.uk

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.

Disclaimer The views expressed in this article, and in the accompanying article (http://dx.doi.org/10.1136/thoraxjnl-2013-203413) do not necessarily represent the personal views or practice of the authors, but have been written to stimulate debate.

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