Commentary

Thrombolysis in pulmonary embolism: are we under-using it?

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Introduction

Pulmonary embolism is a common condition leading to significant morbidity and mortality. Standard initial therapy consists of heparin treatment, which has been shown to improve the outcome. Nevertheless, 3-month mortality remains high, ranging from 10% to 17.5%, and is higher for massive PE.1–3 Thrombolysis for acute PE remains a controversial treatment, due in part to the inadequate evidence demonstrating an improvement in outcome. Current British Thoracic Society (BTS) guidelines for thrombolysis suggest its use only in massive PE, which it defines as ‘one so severe as to cause circulatory collapse’.4 Over the last year, we have experienced four cases of pulmonary embolism that were successfully thrombolysed due to respiratory failure despite being haemodynamically stable. This led us to review some of the evidence for thrombolysis in PE, and this commentary investigates the potential for expanding the role of thrombolysis in this condition, suggesting its use in respiratory failure as well as circulatory failure.

Despite being controversial, thrombolysis has several theoretical advantages over simple anticoagulation with heparin.5 It should promote faster clot lysis. Acutely, this would produce more rapid improvements in pulmonary perfusion and haemodynamic imbalances, but would also reduce chronic vascular obstruction and the potential for pulmonary hypertension. Thrombolysis would also be expected to eliminate venous thrombi, and hence reduce the incidence of recurrent emboli.

Current evidence for thrombolysing only haemodynamically compromising PEs

The BTS guidelines for thrombolysis only for circulatory compromise are based on a present paucity of data.4 In 1995, a very small study looked at 8 patients with shock related to massive PE.6 The four patients receiving heparin died, whereas the four receiving thrombolysis survived, and it is based on this, and the poor outcome in massive PE with shock, that the recommendation is based.

On unselected patients with PE, the evidence for thrombolysis is even less robust. There are only nine such randomized controlled trials of PE thrombolysis vs. heparin, with a combined total of <500 patients.3,5 Several of these have demonstrated more rapid clot resolution and shown more significant angiographic, perfusion scan, and haemodynamic improvements with thrombolysis. Despite this, no significant improvement in mortality or the incidence of recurrent PEs could be demonstrated in any of these studies.3,5 A further meta-analysis of these studies yielded similar findings.3 With this lack of evidence, many authors have found it very difficult to widen the clinical use of thrombolysis in PE.

Several authors have looked for evidence to expand the indications for thrombolysis in PE. Subgroups of patients with documented PE have been examined to search for particular indications. More recently, a subgroup of patients displaying right ventricular dysfunction but with haemodynamic
stability were looked at as candidates for thrombolysis. This subgroup was originally suggested following studies which demonstrated a worse clinical outcome in this patient group. Right ventricular dysfunction was also noted to be associated with a worse outcome in retrospective PE registries. A number of prospective studies have confirmed the prognostic importance of right ventricular dysfunction in pulmonary embolism, even in the subgroups of patients without shock at presentation. Although some studies have not concurred with these findings, right ventricular dysfunction is generally accepted as a predictor of mortality in haemodynamically stable PE. This subgroup has started to be investigated with regard to the potential benefits of thrombolysis. A retrospective study based on data from the Management Strategy and Prognosis of Pulmonary Embolism Registry showed some advantage in survival in thrombolysed patients without shock but with right ventricular dysfunction. This study had several limitations, however, being retrospective and non-randomized. These findings were not replicated by Hamel et al. A more recent randomized study of thrombolysis in 256 patients with preserved systemic blood pressure but right ventricular dysfunction, showed that thrombolysis in these patients led to a reduction in the combined end point of mortality and need for escalation of therapy. Again, no significant change in mortality alone was noted. On the basis of these studies, some authors have suggested that patients should be risk-stratified with echo-cardiography, and thrombolysis used for normotensive patients with pulmonary embolism who have moderate or severe right ventricular dysfunction. Studies are also investigating whether some of the cardiac biomarkers (troponin and brain natriuretic peptide) may be used as surrogates of right ventricular dysfunction and used in such a stratification of risk. At the present moment, however, most authors advocate the use of thrombolysis only in massive PE when there is evidence of circulatory failure, usually taken as a systolic BP <90 mmHg.

### Should the role of thrombolysis in PE be extended?

#### Lack of evidence

The lack of evidence for thrombolysis is not evidence of its failure, and this is one of the issues in our increasingly evidence-based medical practice. To demonstrate benefit of thrombolysis in myocardial infarction, several thousand people had to be enrolled in controlled trials, and this treatment did not become standard practice until nearly 20,000 patients had been studied, and the subgroups that benefit from treatment defined. The studies performed for PEs were not adequately powered to demonstrate mortality differences, and hence were not designed as such. The prospective randomized study by Konstantinides et al. was designed to test a combined end-point including mortality and therapy escalation. Such combined end points have long been accepted as evidence in conditions such as acute coronary syndromes, which are more prevalent than pulmonary emboli. It is interesting to use myocardial infarction as a further parallel concerning the time after symptoms that thrombolysis is given. As is well known, thrombolysis in MI is effective in the first 24 h, but should be given as early as possible. In the randomized trials, the mean duration of PE symptoms before thrombolysis was 3.7 ± 0.2 days. It has been suggested that due to the extensive bronchial collateral circulation, effective thrombolysis for PE can be given over a much longer time period than for the poorly collateralized coronary circulation. Nevertheless, it does ask questions as to whether the randomized studies of thrombolysis in PE have been missing the most effective thrombolytic period. In fact, a study looking at these trials showed that with each additional day of PE symptoms, there was a decreasing efficacy of thrombolysis as measured by reperfusion.

### Which PEs may be candidates for thrombolysis?

We do not suggest that all minor pulmonary emboli be treated with thrombolysis. Well-tolerated PEs have an extremely good prognosis when treated with heparin. Furthermore, thrombolysis does have some inherent risk, particularly of haemorrhage. There is marked variability in the reported incidence of major haemorrhage in studies. This is often defined as fatal haemorrhage, intracranial haemorrhage (ICH), or bleeding that requires either surgery or transfusion. A recent review of studies comparing thrombolytic and heparin therapy showed mean incidences of major haemorrhage of 6.3% and 1.8%, respectively, and of ICH, 1.2% and 0%, respectively. However, the randomized study by Konstantinides et al. showed no increase in the incidence of major bleeding in 256 patients randomized to receive heparin and thrombolysis or heparin and placebo. There were no cases of intracranial haemorrhage in either group, and the only fatal bleed was in the non-thrombolysed group. It is possible that we are being overcautious
in not using thrombolysis for more severe PEs. As described above, some authors have looked at a subgroup of patients displaying right ventricular dysfunction as potential candidates for thrombolysis. In our experience in a district general hospital, four patients were thrombolysed over the course of a year, despite being haemodynamically stable. Strict adherence to the guidelines would have led to thrombolysis not being used. All of our cases had anatomically very large emboli, based on CT pulmonary angiogram (CTPA) (Figures 1 and 2) and severe respiratory failure with an impeding need for mechanical ventilation (average PaO₂ of 7.81 kPa while on maximal amounts of inspired oxygen). All the patients that were thrombolysed were treated with alteplase (tPA) within a few hours of symptom onset. All did extremely well and had arterial saturations >95% on air the next day. There were two instances of minor bleeding (haematuria), but no major or intracranial haemorrhage. Thrombolysis was used in these cases as it was felt that, given the severity of the patient’s condition, the potential benefits of thrombolysis would outweigh the risks. We postulate that severe respiratory failure necessitating further respiratory support may be a useful subgroup to consider when expanding the uses for thrombolysis.

**Thrombolysis for respiratory failure and not just circulatory failure?**

Hypoxia results from large PEs for a number of reasons, including shunting and V/Q mismatch. There is a well-reported relationship between PE severity and PaO₂ or P(A-a)O₂. Among patients studied by McIntyre et al., there was a direct linear relationship between the percentage of the pulmonary vascular bed obstructed (measured by angiography, mPAP and cardiac indices) and the PaO₂. In fact among the seven patients with a PaO₂ < 6.7 kPa, there were six with >50% of their pulmonary vasculature obstructed, as shown by angiography. All these patients had significant pulmonary hypertension, and two died shortly after being studied. There is also some evidence that the outcome is worse following a PE if there is significant hypoxia (< 8 kPa). Indeed, in the recent study by Konstantinides et al., respiratory failure was one of the main indications causing escalation of treatment and rescue thrombolysis. It is noteworthy that a large PE (causing right atrial hypertension) in the presence of a co-existent patent foramen ovale (PFO) may cause further hypoxia due to increased right to left shunting through the PFO. A PFO has also been shown to be an independent predictor of mortality in PEs, and authors have suggested the consideration of thrombolysis in these cases.

As in our cases, escalating oxygen requirements and hypoxia may necessitate mechanical ventilation. This may worsen the situation and produce circulatory collapse for several reasons. Firstly, sedatives may blunt the necessary catecholamine surge and produce vasodilatation. Secondly, lung inflation and the positive pressures can further impair the venous return. Third, mechanical ventilation can increase the pulmonary vascular resistance, which can further decompensate the right ventricle.

We propose that the presence of severe hypoxia necessitating ventilation, in the context of recent PE, may well be an indication for thrombolysis despite the absence of circulatory collapse. This is a subgroup with a worse prognosis, the degree of hypoxia is a marker as to the size of the embolus, and thrombolysis may relieve the need...
of mechanical ventilation, a procedure with many inherent risks. Indeed, this indication for thrombolysis would lend itself well to a district general hospital setting where severe respiratory distress could be promptly treated with thrombolysis, not relying on investigations such as echocardiography to ascertain right ventricular impairment. We feel that similar groups of patients would also benefit from thrombolysis in the future.

Conclusions

Despite appearing an intuitive therapy, thrombolysis for pulmonary emboli is only presently recommended for massive PE with haemodynamic shock. This recommendation has come from a small study of eight patients, coupled with the known high mortality rates of this condition. This commentary postulates that thrombolysis for massive PE may also in the future encompass respiratory failure (e.g. need for mechanical ventilation) as well as circulatory failure. Further large controlled trials are needed in this area.

References