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Should thrombolysis have a greater role in the management of pulmonary embolism?

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ABSTRACT – Pulmonary embolism (PE) continues to be associated with significant mortality despite advances in the diagnostic techniques available for its detection. Anticoagulation remains standard treatment in PE although there is a consensus view that 'step-up' to thrombolytic therapy in addition to anticoagulation is indicated in those patients who are systemically shocked at presentation – a group defined as having suffered 'massive pulmonary embolism'. Considerable research has been directed at attempting to identify further groups of patients with PE who are at high risk of morbidity and mortality – notably those who are labelled as having suffered 'sub-massive pulmonary embolism' where this is defined as the presence of right-heart strain in the absence of systemic shock. In particular, the potential benefit of extending thrombolytic therapy to include those patients with sub-massive PE has been the subject of much enquiry and debate. This review examines the evidence for thrombolytic therapy and explores the potential for risk stratification in PE.

KEY WORDS: computerised tomography pulmonary angiography, pulmonary embolism, right ventricular strain, submassive pulmonary embolism, thrombolysis

Introduction

Over the past 40 years pulmonary embolism (PE) has remained an under-diagnosed and potentially fatal disease despite significant advances in prevention strategies and the diagnostic tools available for its detection. This has been demonstrated in several autopsy series, which have shown that 15% of hospital deaths are caused by, or are associated with, PE.[1–3] In addition, the correct antemortem diagnosis of fatal PE has remained relatively fixed at only 30%.[4,5]

Diagnostic investigations for venous thromboembolic disease (VTE) have advanced significantly in recent years with the advent of multi-slice computerised tomography (CT) scanning, biochemical markers of VTE and the ability to perform reliable echocardiography (ECHO) at the bedside. These advances have not been accompanied by significant developments in the treatment options for PE, however, and anticoagulation remains the mainstay of management with thrombolysis being reserved for patients who are systemically haemodynamically compromised with so-called 'massive pulmonary embolism'. However, massive PE is responsible for only 50% of deaths resulting from PE with the remaining 50% accounted for by two additional sub-groups of patients – those suffering sub-massive PE, defined as evidence of right-heart strain in the absence of systemic haemodynamic compromise, and those suffering recurrent PE.[6]

Considerable attention has been focused on the sub-set of patients with sub-massive PE and a fundamental question has been whether this group may benefit from more aggressive therapy – specifically the use of thrombolytic agents. The utility of measured right ventricular strain as a potential marker for increased mortality in PE and the possible benefit of thrombolysis when this strain is present have been the subject of much research and debate.[7–10] The need for stratification of mortality risk in PE using currently available diagnostic techniques and the possibility for expanding the role of thrombolysis will be discussed in this review.

Pathophysiology of pulmonary embolism

When an embolus lodges in the pulmonary circulation numerous pathophysiological events occur which ultimately lead to increased right ventricular afterload with an associated increase in right ventricular wall stress and oxygen demand. This results in dilatation of the right ventricle and myocardial ischaemia that may lead to hypokinesis and eventual failure. Right ventricular strain also has a synchronous effect on the left ventricle; first, right ventricular dilatation causes septal shift that reduces left ventricular diastolic filling and therefore left ventricular output and secondly, reduced right ventricular output (due to the above mechanisms) will result in diminished left ventricular preload. Systemic cardiac output suffers as a result and so does coronary artery perfusion, thereby exacerbating right ventricular ischaemia.

The degree of physiological disruption from a PE depends upon two main factors – size of the embolus and pre-existing cardiopulmonary function. A patient with compromised cardiopulmonary function is likely to manifest a similar haemodynamic response to the patient who suffers a significantly larger PE on the background of normal cardiopulmonary reserve. This presumably explains why numerous studies have shown that clinical outcome is more accurately predicted by right ventricular failure (as a product of embolus size and cardiopulmonary status) rather than the extent of pulmonary artery thrombus alone.[11–13]

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An exact correlation between mortality risk and the combination of embolus size and pre-existing cardiopulmonary status has been elusive to date although the presence of right ventricular dysfunction, detected by ECHO, has been suggested as a potential marker of severity of PE warranting aggressive treatment with thrombolysis.[14]

However, opponents of thrombolysis observe that a substantial number of patients with PE who have evidence of right ventricular dysfunction do not die. In their view, this observation, together with the inherent risks of thrombolysis, argue against its routine use in sub-massive PE.

An examination of the scientific evidence behind these standpoints follows.

Thrombolysis in pulmonary embolism

Considerable evidence supports the proposition that right ventricular dysfunction (ie sub-massive PE) leads to an increase in mortality. Two large multicentre registries, the International Cooperative Pulmonary Embolism Registry (ICOPER)[15] and the Management Strategies and Prognosis of Pulmonary Embolism Registry (MAPPET),[16] have confirmed that clinical, haemodynamic and echocardiographic findings indicating actual or impending right heart failure (ie massive or submassive PE) independently predict an in-hospital mortality rate of at least 8%. In another study of 317 patients the mortality rate from PE while in hospital and within one year of admission with PE was evaluated for patients with and without echocardiographic evidence of right ventricular dysfunction. For those with evidence of dysfunction the mortality rate was 13% in hospital and after one year and for those without it was just 0.9% (in hospital) and 1.3% (at one year).[17]

There is also strong evidence that thrombolysis rapidly improves physiological parameters both angiographically and haemodynamically in PE. In 1971, Miller and colleagues demonstrated that thrombolysis significantly reduced pulmonary artery pressure as well as the amount of pulmonary arterial thrombus shown on pulmonary angiography.[18] This was supported by the Urokinase Pulmonary Embolism Trial (UPET) study which showed urokinase to be superior to heparin in clot resolution on angiography over the first 24 hours (24% resolution with urokinase, 8% with heparin).[19] This benefit failed to be maintained, however, and after two weeks urokinase and heparin were found to be equally effective (55.4% for thrombolysis *v* 56.2% for heparin) and similarly after one year (78.8% *v* 77.2%). Critics therefore argue that there are no long-term benefits in using thrombolysis with regards to reducing the risk of progression to chronic pulmonary hypertension caused by unresolved intra-arterial thrombus. However, a recent study has challenged this belief. In 2006, Nijkeuter and colleagues investigated a group of patients with confirmed PE and found 68% with evidence of residual pulmonary arterial thrombus after six weeks of anticoagulation. In addition, their reported figures for persistent thrombus at three months, six months and 11 months were 65%, 57% and 52% respectively.[20] The evidence regarding the relative efficacy of thrombolysis compared with anticoagulation as far as long-term pulmonary artery revascularisation is concerned therefore appears to be incomplete and is a matter of continuing debate.

The evidence examining the efficacy of thrombolysis in terms of clinical outcomes is less convincing. In the UPET study the improvement in the speed of resolution of pulmonary artery thrombi was not accompanied by a significant improvement in mortality (7.3% in urokinase group and 9.0% with heparin) or in the rate of recurrent PE (17.1% *v* 23.1% respectively).[19] Moreover, severity of the embolism and primary outcomes were assessed on angiographic rather than clinical criteria. UPET failed to identify a patient sub-group that might benefit from thrombolysis and did not show improved clinical outcomes in patients who were thrombolysed.

In 1993, Goldhaber and colleagues revisited this issue and compared thrombolysis with anticoagulation in the management of PE.[14] Alteplase (100 mg infusion over two hours) followed by heparin was compared with heparin treatment alone in 101 patients. Echocardiographic evidence of right ventricular strain was assessed and found to be present in 54% of the patients who were randomly selected for study, but it is important to note that the absence of right ventricular strain did not preclude patients from being enrolled. Although rapid improvement in right ventricular dysfunction was observed in the thrombolysis group, this was not accompanied by a significant mortality benefit. Patients at low risk of death were included in the study and the overall mortality rate observed was only 2%, which might partially explain this apparent discrepancy in outcomes. In any event, Goldhaber and colleagues subsequently proposed that the presence of right ventricular dysfunction might define a high-risk group of patients worthy of independent study with thrombolysis.

In the only randomised trial to date that compares heparin with thrombolysis in patients with echocardiographic evidence of right ventricular dysfunction without shock,[21] there was a significant reduction in the primary end-point from 25% for treatment with heparin alone to 11% for thrombolysis. However, the primary end-point studied was not mortality but a combination of in-hospital death and clinical deterioration requiring an escalation of treatment. There was no observed significant reduction in mortality itself. Critics of this paper argue that the primary end-point was insufficiently robust to provide support for thrombolysis and emphasise that no significant difference was shown in either mortality or the rate of recurrent PE.[22] In addition, it has been shown that recurrent PE is the main cause of death in patients who are haemodynamically stable when therapy is begun,[23] and that thrombolysis fails to reduce the risk of recurrent PE.[19,21,24,25]

A comprehensive meta-analysis reviewing the use of thrombolysis in PE was conducted by Wan and colleagues. It identified 11 trials involving 748 patients.[26] Of these 11 trials:

- five excluded patients with systemic shock
- one specifically examined patients with shock[27]
- one investigated patients without shock but with evidence of either right heart strain or pulmonary hypertension.[21]

This meta-analysis failed to find a significant reduction in recurrent PE and in mortality when thrombolysis was compared with heparin (6.7% *v* 9.6%) in unselected patients with acute PE. On the other hand, thrombolysis was superior in those trials that included haemodynamically unstable patients (9.4% thrombolysis, 19.0% heparin). Importantly, the meta-analysis found no significant increase in major bleeding in patients who were thrombolysed. The authors concluded that, although there is no evidence for thrombolysis in unselected patients with acute PE, a benefit is suggested in those at highest risk of recurrence or death. The individual trials studied enrolled only modest numbers of patients and it is likely that none of them was sufficiently powered to detect a true mortality advantage for a particular treatment. Moreover, the design of all but one of the trials did not allow for the detection of a high-risk group that might benefit from thrombolysis.[21]

Future risk stratification for the severity of pulmonary embolism

The British Thoracic Society guidelines recommend the use of thrombolysis in the treatment of massive PE, but advise against its use in sub-massive PE due to the risk of haemorrhage and the absence of proof for a survival advantage.[28]

Right ventricular dysfunction as diagnosed by ECHO has been shown in numerous trials to predict increased mortality in normotensive patients. Three reports demonstrated a fourfold increase in mortality rate for patients who were not systemically shocked but who had echocardiographic evidence of right ventricular dysfunction and a recent analysis of 1,035 patients enrolled in the ICOPER demonstrated that right ventricular hypokinesis remained an independent predictor of 30-day mortality.[7–9,29] The logistical difficulties of providing accurate ECHO at all times of day and the technical problems associated with obtaining good quality transthoracic imaging have, however, raised the question about the need for additional imaging and non-imaging tests to provide alternative or supplementary evidence of impending right ventricular failure and so enable accurate risk stratification.

Recent advances in multidetector row chest CT have shown that right ventricular enlargement on reconstructed four chamber views of the heart is able to predict increased mortality – in one retrospective study of 431 patients, mortality at 30 days was found to be 15.6% in patients with right ventricular enlargement compared with 7.7% in those without.[30] These findings offer the possibility of using an imaging technique that is capable of both diagnosing PE and estimating its mortality risk with the additional potential for accurate guidance in step-up of treatment to thrombolysis.

Cardiac biomarkers have been posited as possible tools for risk stratification in PE. There is evidence that the absolute troponin level in acute PE correlates with severity of right ventricular dysfunction.[31–35] The MAPPET-2 study was a prospective, multicentre trial intended to evaluate the usefulness of troponin elevation in determining the prognosis of patients with acute PE.[32] Patients with an elevated troponin I had a mortality risk 17 times greater than patients with no troponin rise. These findings have since been confirmed by other workers.[36–39] Despite this the positive predictive value of troponin for in-hospital death is relatively low (12 to 40%). Conversely, its negative predictive value for in-hospital death is very high (97 to 100%), thereby allowing it to be reliably used to rule out an adverse event in acute PE but making it of little benefit for ruling it in.[40]

Elevated levels of brain natriuretic peptide (BNP) and N-terminal fragment proBNP (NT-proBNP) are also associated with right ventricular dysfunction in acute PE.[41–46] Once again, these markers have sensitivity (negative prognostic value) approaching 100% but low specificity (12 to 25%) in predicting in-hospital death.[40]

In order to improve the sensitivity and specificity of these tests Kucher and Goldhaber proposed a risk stratification algorithm (Fig 1) and this has received support from two recent studies. Binder *et al* investigated 124 patients with PE and found more than a 12-fold increase of in-hospital death or complication risk in those with a combination of elevated NT-proBNP and an abnormal ECHO and a 10-fold increase in the same adverse outcomes in those patients with an elevated troponin together with an abnormal ECHO.[47] Secondly, a retrospective analysis of 141 patients conducted by Scridon *et al* has demonstrated that the combination of elevated troponin with right ventricular enlargement predicted higher mortality even in normotensive patients.[48]

Conclusion

The role for thrombolysis in the management of PE remains controversial. There is, however, growing evidence that a sub-set of haemodynamically stable patients with right ventricular failure may benefit from this more aggressive treatment option

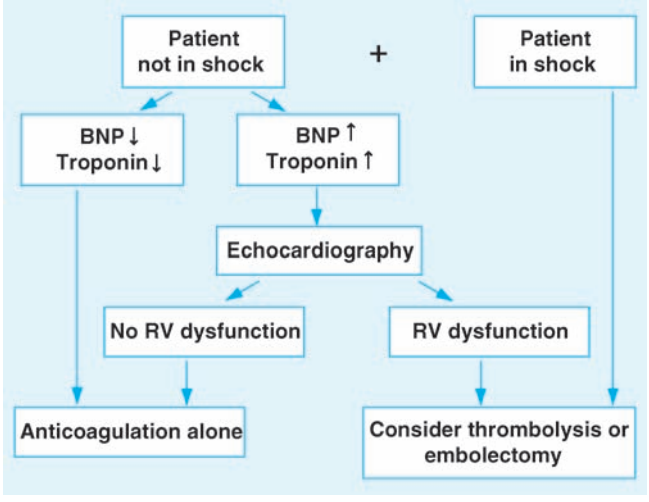

Fig 1. Possible risk stratification algorithm for pulmonary embolism proposed by Kucher and Goldhaber.[40] BNP = brain natriuretic peptide; RV = right ventricular. Reproduced with permission from Wolters Kluwer Health.

and the advent of increasingly sophisticated diagnostic tools may facilitate the development of algorithms effective in identifying the cohort of patients suffering PE who have an increased mortality risk. Many critics are also concerned regarding the morbidity associated with thrombolytic therapy, but it is worth noting that the current trials do not show an increase in significant haemorrhage following thrombolysis.[26] Essentially, there is a fundamental need for a scientifically robust trial to test the benefits of thrombolysis and such a trial would need to be sufficiently powered to produce reliable data on the crucial clinical end-points of mortality and rate of PE recurrence. This ideal approach is challenging – variation in clinical presentation, difficulties in diagnosis, variable severity of the condition, and the multitude of medical specialties that care for these patients all contribute to the difficulties inherent in the design of such a study. Regardless of the feasibility of conducting the ideal clinical study, further debate is required to decide the level of evidence permissible to allow publication of risk-benefit guidelines for a form of therapy that is undoubtedly lifesaving in some patients with PE.

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