New therapies

Pulmonary embolism—the role of thrombolytic therapy in its management

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Summary
In massive pulmonary embolism where there may be evidence of right ventricular dysfunction and acute pulmonary hypertension, anticoagulation therapy alone may prove inadequate. In such situations use of thrombolytic agents produces an improvement in haemodynamics compared to anticoagulants alone, although studies to date have been too small to address the issue of mortality benefit. It would appear that all age groups gain benefit from the use of thrombolics. Studies that have compared thrombolytic agents and anticoagulants are discussed. In addition, the issues of the choice of thrombolytic agent and the different modes of delivery of therapy are addressed.

Keywords: pulmonary embolism, thrombolysis, anticoagulation

Pulmonary embolism is a commonly encountered disorder, often precipitated by deep venous thrombosis. Venous thromboembolism is the third most common cardiovascular disorder after acute coronary syndromes and stroke, with 300 000 hospitalisations and 50 000 deaths annually in the US alone.1 The true incidence is probably much higher with many cases going undiagnosed. It can result in pulmonary hypertension and right ventricular dysfunction and has a mortality rate of approximately 14%.2

Diagnosis
The diagnosis can frequently be made on the basis of the clinical presentation. This usually involves an acute onset of pleuritic pain associated with shortness of breath and perhaps haemoptysis. A preceding history of deep venous thrombosis may be present. The patient usually has a tachycardia, is tachypnoeic and may be hypoxic and hypotensive. Depending on the size of the pulmonary embolus the electrocardiogram may show transient features of acute right heart strain with right axis deviation and right bundle branch block.3 In addition the frequently quoted S, Q, T changes may be evident. The diagnosis can usually be confirmed by ventilation/perfusion scans (a ventilation/perfusion mismatch being indicative of a pulmonary embolus) or pulmonary angiography (the 'gold standard' see figure). Other possible means of confirming the diagnosis include the use of echocardiography (including transoesophageal echocardiography) to detect thrombus directly in the pulmonary trunk and proximal parts of each pulmonary artery.4

Consequences of pulmonary embolism
The haemodynamic response to pulmonary embolism depends upon a number of factors including the size of the embolus, any coexistent cardiopulmonary disease, and the neurohumeral responses produced. An acute increase in right ventricular afterload occurs when approximately 25% of total pulmonary blood flow is acutely obstructed.5 Although right ventricular systolic pressure continues to rise as the degree of obstruction increases it is usually unable to generate a maximum mean pulmonary artery pressure above 30 mmHg.5 Thus as afterload continues to increase, the right ventricle begins to fail and right atrial pressure rises; when forward cardiac output can no longer be sustained clinical shock occurs. Acute mortality correlates with the presence of systemic hypotension, implying that right heart functional reserve is the major determinant of acute survival.6 Longer term mortality, however, is dependent to a major degree on co-existent cardiopulmonary disease.7

Treatment
Standard therapy in the past consisted of anticoagulation, initially with intravenous heparin and subsequently with warfarin. Barratt and Kordan first reported on the mortality benefit of anticoagulation in pulmonary embolism. They observed no deaths in 54 patients treated with anticoagulants (intravenous heparin over 36 hours and nicoumalone for 14 days) whilst there were five deaths in 19 control patients who did not receive any anticoagulants.8 The rationale for anticoagulation is to provide prophylaxis against further thromboembolic events during the period of time that the body’s own fibrinolytic system is gradually lysing the embolus.2 In contrast, the theory behind the use of thrombolytic therapy (followed by anticoagulation) for pulmonary embolism is that thrombolysis, by actively dissolving formed clot, would restore cardiopulmonary function to normal more quickly. In addition chronic pulmonary hypertension may also be reduced and the source of embolus in the venous system may be
removed or reduced. Thrombolysis would thus be particularly beneficial in massive pulmonary embolism associated with haemodynamic compromise. The only alternative treatment available for such patients previously would have been pulmonary embolectomy, a procedure available in only a limited number of hospitals.

In patients with major pulmonary embolism, anticoagulation alone may fail to resolve pulmonary artery clot completely in 75% of patients at 1–4 weeks, and in 50% at four months. The thrombolytic agents urokinase and streptokinase were first approved for the treatment of pulmonary embolism in 1977. Urokinase was approved in a dose of 2000 U/lb as a bolus followed by 2000U/lb hourly for 12 to 24 h, whilst streptokinase was approved as a fixed bolus of 250 000 U followed by 100 000 U/h for 24 h. Several small early uncontrolled studies showed that streptokinase delivered either locally via a pulmonary artery catheter or peripherally appeared to produce angiographic and clinical improvement. The doses used varied with an initial bolus (over 15–60 min) of 160 000–600 000 U and a maintenance infusion of 90 000–150 000 U for up to 72 h. A number of different dosage regimes of urokinase have been reported to be effective in producing haemodynamic and angiographic improvement including low-dose short infusions of urokinase (200 000–300 000 U over two hours given to nine patients, which resulted in good clinical response in seven of them).

**THROMBOLYSIS vs ANTICOAGULATION**

Although there have been several clinical studies comparing thrombolytic therapy and anticoagulants alone, these studies had limited patient numbers. All the early studies demonstrated a more rapid anatomical or physiological improvement in thrombolysis-treated patients, but because of the small sample sizes the effects on mortality could not be determined.

One of the larger early studies, the phase I portion of the Urokinase Pulmonary Embolism Trial (UPET), compared heparin alone with urokinase (12 h infusion) in 160 patients with angiographically proven pulmonary embolism. Although 24 h post-commencement of therapy the urokinase-treated group had significantly greater haemodynamic and anatomical improvements than the heparin-treated patients, by five to seven days post-treatment no difference between the two groups was noted on lung scans. In addition, during the two weeks following therapy, there was a trend towards fewer recurrent pulmonary emboli in the urokinase-treated patients (17% vs 23%). The benefits of thrombolytic therapy, however, were achieved at a cost, namely increased bleeding complications (27% incidence of severe bleeding, defined as a fall in haematocrit of more than 10%, and/or need for a blood transfusion of more than two units). Small studies that utilised either centrally or peripherally administered streptokinase showed evidence of increased thrombolysis both clinically and angiographically when compared to heparin administration alone.

Two early small studies (13 and 15 patients) which compared heparin alone with tissue plasminogen activator (tPA), 25–80 mg given over 40–90 min, plus heparin, noted a modest early improvement in total pulmonary resistance and arterial oxygen saturations in the tPA-treated patients. However, pulmonary angiograms two hours post-treatment showed no significant difference and lung scans 24-h post-treatment only showed a trend towards greater improvement with tPA. In the PAIMS 2 study 36 patients were randomised to a two-hour infusion of recombinant tPA (rtPA) followed by heparin, versus heparin alone. The mean pulmonary artery pressure at two hours decreased significantly in the rtPA plus heparin group but not in the heparin alone group. Lung scans at days 7 and 30, however, were not dissimilar in the two groups. In a larger, more recent, study Goldhaber and colleagues randomised 101 haemodynamically stable patients with pulmonary embolus such that 46 received rtPA (100 mg over two hours) and 55 heparin alone. In 39% of rtPA-treated patients (cf 17% of the heparin-treated group) right ventricular wall motion improved at 24 h. Pulmonary perfusion also improved by 14.6% compared to 1.5%. No clinical episodes of recurrence occurred in their rtPA group whereas five of the heparin group had recurrent episodes within 14 days.

**THE ROLE OF tPA**

Experimental studies of venous thromboembolism which appeared to suggest that tPA was more potent than urokinase or streptokinase prompted the clinical assessment of tPA in pulmonary embolism first reported in 1981, and its use in pulmonary embolism in 1985. A 65-year-old man received 30 mg of rtPA over 90 minutes via a catheter inserted into the right ventricle. Pulmonary angiography 90 minutes later demonstrated

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**Box 1**

**Management options in pulmonary embolism**

- conventional anticoagulation—iv heparin followed by warfarin for 3 months
- thrombolytic therapy (streptokinase, urokinase or tPA) followed by anticoagulation
- pulmonary embolectomy

**Box 2**

**Indications for thrombolytic therapy**

- massive pulmonary embolism—as first line therapy
- failure of patient to respond to a conventional anticoagulation regime

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**Figure** Pulmonary angiogram obtained using a pulmonary artery catheter. Multiple intraluminal clots are present (arrows) in the left upper and lower lobe pulmonary arteries.
recanalisation. In 1986, Braunwald’s group reported on 30 patients with angiographically proven pulmonary embolism (segmental or more proximal pulmonary artery involved) presenting within five days of onset of initial symptoms. These individuals received 50 mg of rtPA peripherally over two hours. Pulmonary angiography was repeated immediately after completion of the infusion. If significant clot lysis was evident then routine measures including anticoagulation were continued. If no significant clot lysis was seen, an additional 40 mg of rtPA was administered over 10 hours with repeat angiogram. Overall 28 patients had evidence of clot lysis after treatment with rtPA with qualitative improvement noted by 83%. Mean pulmonary artery pressures decreased significantly from 21 to 18 mmHg and right ventricular dysfunction on echocardiography resolved rapidly in some patients. Only one of the treated patients had major bleeding complications. The US Food and Drug Administration approved use of rtPA for acute pulmonary embolism (100 mg given intravenously over two hours) in 1990.

COMPARISON OF THROMBOLYTIC AGENTS

Only limited information is available comparing different thrombolytic agents in the treatment of pulmonary embolism. In the phase II portion of UPET, regimes comprising 12 h of urokinase, 24 h of streptokinase, or 24 h of streptokinase (250 000 U bolus and 100 000 U/h for 24 h) were compared in 167 patients. No differences in mortality or angiographic resolution were noted in the three groups.

Goldhaber et al conducted a randomised study of 90 patients comparing 100 mg rtPA (over two hours) with urokinase (3 × 10⁶ U over two hours, with the initial 1 × 10⁶ U given as a bolus over 10 min). Both drugs were administered peripherally and all the recruited cases had angiographically proven pulmonary embolism. In 87 patients repeat pulmonary angiograms were available at two hours. In the rtPA group 79% showed angiographic improvement compared to 67% of the urokinase group but this difference was not significant. Furthermore perfusion lung scans at 24 hours were similar in the two groups. The European Cooperative Study Group for Pulmonary Embolism assessed 63 patients randomised to urokinase (4400 U/kg bolus, 4400 U/kg hourly for 12 h) or rtPA (10 mg bolus, 90 mg over two hours) followed by heparin. The decrease in total pulmonary resistance at 12 h was similar in the two groups (53% and 48%, respectively). Bleeding complications were also similar in the two groups.

BOLUS REGIMES

Animal experiments have previously shown that thrombolysis continues for some time after tPA is cleared from the circulation and that thrombolysis can be accelerated and increased with reduced bleeding if tPA is administered over a short period. In a study of bolus therapy 38 patients were randomised to receive either a two-minute infusion of rtPA (0.6 mg/kg) or saline placebo in addition to a standard heparin infusion regime. Of the actively treated patients 34% had a greater than 50% resolution in perfusion defects at 24 h compared to only 12%, of the placebo-treated group. However, this difference was no longer apparent in lung scans carried out at seven days. No major bleeding complications were noted in the rtPA-treated patients.

In a prospective open trial, 54 patients with massive pulmonary embolism received a 10-min infusion of rtPA at a dose of 1 mg/kg. At 48 h and 10 days there was an absolute improvement in the perfusion defect of 11% and 31%, respectively. One of the patients died of an intracranial haemorrhage.

Published studies of bolus regimes using urokinase or streptokinase are few in number. Two small open studies that used boluses of 15 000 U/kg and 20 000 U/kg of urokinase observed both angiographic improvement and a reduction of pulmonary artery pressure, with a low incidence of major bleeding complications. There are, however, no published studies to date comparing bolus and other administration regimes.

LOCAL THERAPY

Thrombolytic therapy can be administered centrally rather than peripherally, using catheters sited in either the right ventricle or in the pulmonary circulation itself. In theory this should result in higher local concentrations of thrombolytic agent at the site of the pulmonary embolus and may minimise bleeding complications. Several of the early studies that used streptokinase involved locally delivered therapy over several hours (up to 72 h). In a non-randomised study of 10 patients with massive pulmonary embolus, treatment comprised intrapulmonary thrombolytic therapy (urokinase or streptokinase), anticoagulation and Greenfield filters. A rapid response was seen in all with
significant improvements in oxygen saturation, pulmonary artery pressures, cardiac output and blood pressure compared to 10 comparable patients over the same time period who had received heparin alone. Low-dose streptokinase (10 000 U/h for 15–30 h) delivered locally may also produce rapid lysis.46

In a brief recent report three patients with massive pulmonary embolism that were treated with centrally administered tPA all responded with rapid improvement of pulmonary artery pressures, and marked reduction of chest pain and shortness of breath.47 However, Verstreeta and colleagues, who compared peripheral intravenous versus local pulmonary administration of rtPA in 34 patients, noted that local pulmonary delivery did not appear to confer any advantage. Similar rates of lysis, bleeding and induction of systemic lytic state were observed.46

**SPECIAL CASES**

Special protocols which theoretically allow more gradual thrombolysis have been suggested for treating massive pulmonary embolus in patients who have undergone recent surgery. One group has suggested a regime comprising of a bolus of urokinase (2200 U/kg) injected directly into the clot via a catheter positioned in the pulmonary artery, to be followed by a continuous infusion of urokinase at 2200 U/kg hourly until the clot is lysed (infusion duration up to a maximum of 24 h).47 Heparin is administered simultaneously via a peripheral vein at 500 U/h. However, there are no comparative data or studies with more conventional thrombolytic regimes to suggest that regimes similar to the one described above are any safer. Adjuvant measures to thrombolysis, such as cardiopulmonary bypass, may have a role to play in the treatment of specific patients with massive pulmonary embolus who present with cardiac arrest.48

From the studies carried out to date thrombolytic therapy (whether it be streptokinase, urokinase or tPA) appears to be effective in all age groups for the treatment of massive pulmonary embolism. Elderly patients (ie, >70 years) gained similar benefits to younger patients without an increased incidence of major bleeding complications48 when thrombokinase was administered in a regime comprising 250 000 U over 15 min and an infusion of 100 000 U/h for 12 h.

**Conclusion**

Thrombolytic therapy should be considered in all patients with massive pulmonary embolism where there may be evidence of acute pulmonary hypertension, right ventricular dysfunction and possibly systemic hypotension. Although the studies to date have been too small to address the issue of mortality benefit there does appear to be objective evidence of haemodynamic benefit over that achieved by anticoagulation alone. Thrombolysis also apparently reduces the incidence of early recurrence of pulmonary embolism. All age groups and postoperative patients also seem to benefit. Bolus and front-loaded regimes (ie, administered over two or less hours) are simpler to use and appear as effective as longer duration regimes. The decision stage to use any major difference in efficacy between the different thrombolytic agents. Streptokinase should be avoided in those individuals who have received it previously for whatever indication, because of the likely presence of neutralisation antibodies.50

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