Management of massive pulmonary embolism: a retrospective single-centre cohort study

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Background: Massive pulmonary embolism (PE) (PE associated with hypotension or shock) is a condition with a mortality rate in excess of 50%. Although expert opinion favouring thrombolysis exists, this is based predominantly on studies demonstrating physiological benefits rather than a mortality benefit. The optimal treatment for massive PE remains unclear. The majority of studies to date have studied medical therapy, and case series of surgical pulmonary embolectomy have also been reported. No studies directly comparing mortality between medical and surgical therapies have been published. In our institution, both medical and surgical therapies are used in the treatment of massive PE.

Objective: To identify the characteristics and outcomes of patients who received thrombolysis, surgical embolectomy or heparin anticoagulation for management of massive PE.

Design and setting: Retrospective cohort study of patients with massive PE at the Royal North Shore Hospital, Sydney, Australia. The hospital medical records database was searched from 1 January 1996 to 31 December 2006. In addition, both the intensive care and cardiothoracic surgery databases were searched for the diagnosis of PE. Patients were included in our study if there was an ICD-9 diagnosis of PE and a review of notes indicated that the criteria for massive PE were met.

Results: Fifty-one patients with massive PE were identified. Nine received embolectomy, 10 thrombolysis and 14 heparin anticoagulation. There were no statistically significant differences in mortality between these three groups, although resource utilisation was higher in the embolectomy group. Eighteen patients received no definitive treatment because of the poor prognosis of their underlying disease. All patients who received no definitive therapy died.

Conclusions: Massive PE has a high mortality. No significant mortality benefit was associated with any particular therapy. Patients for whom thrombolysis and/or embolectomy are contraindicated may benefit from simple anticoagulation.

Pulmonary embolism (PE) is a common and potentially life-threatening condition. It has an approximate incidence in
Although patients with high-risk PE can be identified and expert guidelines are available, the evidence base for management is limited and the optimal management strategy is yet to be clearly defined. Our study was undertaken to identify the characteristics and outcomes of patients who received thrombolysis, surgical embolectomy or heparin for management of massive PE.

Methods

We conducted a retrospective cohort study at the Royal North Shore Hospital, Sydney, Australia, a 547-bed tertiary referral hospital serving a local population of about 1 million. The study was approved by the Northern Sydney Health Human Research Ethics Committee. The need for informed consent was waived.

Patients diagnosed with PE (according to the International classification of diseases, 9th revision) were identified from a search of the hospital medical records database from 1 January 1996 to 31 December 2006. A further search of the database was undertaken to identify patients who had undergone surgical pulmonary embolectomy. In addition, both the intensive care and the cardiothoracic surgery databases were searched for the diagnosis of PE, to reduce the chance of failing to identify PE patients because of coding errors. Records were reviewed by a single trained data extractor using a specially designed data collection form with a prespecified protocol and predefined definitions. Massive PE was defined as PE associated with hypotension (systolic blood pressure <90 mmHg) and shock (evidence of tissue hypoperfusion).

Records were reviewed for age, sex, presence of malignancy, congestive heart failure and chronic obstructive pulmonary disease. We noted features relating to the presentation, including the presence of cardiac or respiratory arrest, hypotension (systolic blood pressure <90 mmHg), shock, tachypnoea (respiratory rate >20 breaths/min) and right ventricular dilatation and impaired function on echocardiography. We also recorded factors that gave strong relative or absolute contraindications to medical therapy, such as allergy (including heparin-induced thrombocytopenic and thrombotic syndrome), intracranial pathology, recent surgery and active or recent haemorrhage. Sixteen of the patients presented in cardiac arrest. Preoperative troponin levels were measured in five patients (median, 0.11 μg/L; range, 0.01–0.54 μg/L). Echocardiography was performed in all patients, and in each case demonstrated right ventricular dilatation and dysfunction. All patients had contraindications to thrombolytic therapy and all satisfied criteria for massive PE. Their in-hospital mortality was 66% (6/9). Of the patients who died, four died from PE despite embolectomy, one died from bleeding in the postoperative period, and one died from multiorgan failure 30 days after presentation. One patient out of the four who received cardiopulmonary resuscitation survived. IVC filters were inserted in four patients who underwent surgical embolectomy (three survived to leave hospital and one survived 30 days).

Results

We identified 51 patients who satisfied the criteria for massive PE. The primary therapy for PE was surgical pulmonary embolectomy in nine patients, thrombolysis in 10 patients, and therapeutic anticoagulation using an unfractionated heparin infusion in 14 patients. Characteristics of patients who received therapy, as well as investigations and outcomes, are summarised in Tables 1, 2 and 3. Eighteen patients received no definitive therapy.

Surgical embolectomy

Nine patients received surgical embolectomy. All were hypotensive, and four presented in cardiac arrest. Preoperative troponin levels were measured in five patients (median, 0.11 μg/L; range, 0.01–0.54 μg/L). Echocardiography was performed in all patients, and in each case demonstrated right ventricular dilatation and dysfunction. All patients had contraindications to thrombolytic therapy and all satisfied criteria for massive PE. Their in-hospital mortality was 66% (6/9). Of the patients who died, four died from PE despite embolectomy, one died from bleeding in the postoperative period, and one died from multiorgan failure 30 days after presentation. One patient out of the four who received cardiopulmonary resuscitation survived. IVC filters were inserted in four patients who underwent surgical embolectomy (three survived to leave hospital and one survived 30 days).

Thrombolysis

Among the 10 patients who received thrombolysis, in-hospital mortality was 60% (6/10). All patients were hypotensive, and four presented in cardiac arrest. Troponin levels were measured in eight patients (median, 0.10 μg/L; range, 0.01–0.86 μg/L). Echocardiography was performed in nine patients,
and eight patients had documented right ventricular dilatation and dysfunction (for the remaining patient, there was no comment on the right ventricle recorded in the notes). Compared with patients who received embolectomy, those who received thrombolysis had a significantly shorter ICU length of stay ($P=0.01$), shorter duration of mechanical ventilation ($P=0.005$), and fewer haemorrhagic complications ($P=0.02$). Of the patients who died, five died from the initial PE despite thrombolysis, and one died from recurrent PE following thrombolysis. One patient of the four who required cardiopulmonary resuscitation survived. IVC filters were inserted in two patients who survived and had DVT on venous duplex ultrasound scan. One patient did not receive an IVC filter despite the presence of DVT, and subsequently died of recurrent PE.

**Anticoagulation**

Fourteen patients received intravenous anticoagulation with unfractionated heparin alone for massive PE. All patients were hypotensive, and four presented in cardiac arrest. Troponin levels were measured in 10 patients (median, $0.04\mu g/L$; range, $0.01–0.08\mu g/L$). Echocardiography was performed in 11 patients, of whom 10 had documented right ventricular dilatation and dysfunction and one had no comment on the right ventricle recorded in the notes. Significant contraindications to thrombolysis or pulmonary embolectomy (including recent surgery, intracranial pathology or recent or active haemorrhage) were present in this group. Overall in-hospital mortality in this group (36% [5/14]) was not significantly different from mortality in the other groups. All five deaths resulted from the initial PE. Two patients out of four who required cardiopulmonary resuscitation survived. Compared with

**Table 1. Demographics, underlying disease, presentation and treatment-modifying factors in patients with massive PE, by treatment type**

<table>
<thead>
<tr>
<th>Characteristic/factor</th>
<th>Embolectomy ($n=9$)</th>
<th>Thrombolysis ($n=10$)</th>
<th>Anticoagulation ($n=14$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (IQR) in years</td>
<td>62 (31–81)</td>
<td>68 (30–83)</td>
<td>61 (27–82)</td>
</tr>
<tr>
<td>Male : female ratio</td>
<td>5 : 4</td>
<td>8 : 2</td>
<td>6 : 8</td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>1</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>COPD</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Presentation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Preceding syncope</td>
<td>3</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Right ventricular dysfunction*</td>
<td>9</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Treatment-modifying factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergy</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Recent surgery</td>
<td>9</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Recent haemorrhage</td>
<td>4</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Intracranial pathology</td>
<td>4</td>
<td>0</td>
<td>6</td>
</tr>
</tbody>
</table>

COPD = chronic obstructive pulmonary disease. IQR = interquartile range. PE = pulmonary embolism.

* Right ventricular dysfunction was defined by echocardiographic features of the right ventricle. All patients with right ventricular dysfunction had a transthoracic echocardiogram performed.

**Table 2. Investigations undertaken to confirm diagnosis of pulmonary embolism, by treatment type**

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Embolectomy ($n=9$)</th>
<th>Thrombolysis ($n=10$)</th>
<th>Anticoagulation ($n=14$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTPA</td>
<td>5</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>V/Q scan</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Formal angiogram</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>1*</td>
<td>2†</td>
<td>1†</td>
</tr>
</tbody>
</table>

CTPA = computed tomography pulmonary angiogram. V/Q scan = ventilation/perfusion scan.

* Suspected by echocardiography and confirmed at operation. † Suspected by positive venous Doppler study and echocardiography and confirmed at postmortem examination.

**Table 3. Outcome and complications of therapy in patients with massive pulmonary embolism, by treatment type**

<table>
<thead>
<tr>
<th>Outcome/complication</th>
<th>Embolectomy ($n=9$)</th>
<th>Thrombolysis ($n=10$)</th>
<th>Anticoagulation ($n=14$)</th>
<th>$P^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital mortality</td>
<td>6 (66%)</td>
<td>6 (60%)</td>
<td>5 (36%)</td>
<td>0.34</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>0.02</td>
</tr>
<tr>
<td>Median duration of mechanical ventilation in days (IQR)</td>
<td>2 (1–3)</td>
<td>1 (0–1)</td>
<td>0 (0–1)</td>
<td>0.005</td>
</tr>
<tr>
<td>Median ICU length of stay in days (IQR)</td>
<td>6 (1–10)</td>
<td>1 (0–1)</td>
<td>1 (1–3)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

ICU = intensive care unit. IQR = interquartile range. * Considered statistically significant if $P<0.05$. 

**Table 2 continued.**
patients who underwent surgical embolectomy, patients who received anticoagulation had significantly shorter ICU length of stay ($P=0.01$), shorter median duration of ventilation ($P=0.005$), and fewer haemorrhagic complications ($P=0.02$). IVC filters were inserted in five patients who survived and had DVT on venous duplex ultrasound scan.

**Discussion**

We conducted a single-centre retrospective cohort study to describe the outcomes and characteristics of patients with massive PE. In-hospital mortality was 70% overall, but 52% among actively treated patients (ie, excluding patients who received only palliative care). There was no difference in mortality between any treatment strategy. The incidence of haemorrhage, ICU length of stay and duration of mechanical ventilation were significantly greater in patients who had pulmonary embolectomy compared with those who had thrombolysis or anticoagulation.

The overall mortality of 52% in actively managed patients compares with a mortality of 52.4% reported in the massive PE subset from the ICOPER database. Similarly to the present work, this retrospective database demonstrated no reduction in mortality associated with thrombolysis over heparin treatment alone. A recent Cochrane review of the effectiveness of thrombolytic therapy in PE found a significant improvement in haemodynamic variables as judged by echocardiographic features and lung perfusion scanning, but no difference in mortality. Another multicentre retrospective study of all cases of acute PE found that in patients presenting with a systolic blood pressure less than 90mmHg, mortality was 33% with thrombolysis and 26% without thrombolysis (a difference that was not statistically significant). Unlike the present study, these studies demonstrated that thrombolysis was associated with a significantly increased risk of bleeding. The only RCT to demonstrate a mortality benefit from thrombolysis was performed in eight patients, of whom half received thrombolytic treatment and half received heparin alone. All patients in the thrombolysis arm survived but all those in the heparin arm died. However, the small sample size and other methodological weaknesses limit the interpretation of the study: the diagnosis of PE was presumed from the clinical scenario, rather than confirmed, and patients in the control arm were recruited to the study after having recurrent PE on heparin, whereas those in the active treatment arm had thrombolysis following their initial presentation with PE. Other trials comparing thrombolysis with heparin have used angiography to measure surrogate end points, including haemodynamic parameters or reduction of thrombotic burden, in order to demonstrate a benefit of thrombolysis. These trials had a low number of patients with massive PE, making it difficult to ascertain any benefit for this particular population.

Thus, overall, aside from one small study with significant methodological problems, the literature does not support a mortality benefit for thrombolysis over heparin in massive PE. Our results are in agreement with this, but the fact that we conducted a single-centre, retrospective, small study, potentially confounded by selection bias, limits the conclusions that can be reached.

In our study there was no demonstrable mortality difference between patients managed with pulmonary embolectomy and either thrombolysis or heparin alone. Historically, pulmonary embolectomy was reserved as rescue therapy for patients unresponsive to other therapies, and was associated with a mortality of over 50%. There are no RCTs comparing outcomes from surgical embolectomy with thrombolysis or anticoagulation alone. However, one retrospective study comparing embolectomy with thrombolysis found that there was no mortality difference between the two groups. In our study, mortality associated with embolectomy was 66%. Other retrospective series of pulmonary embolectomy in massive PE have demonstrated mortality rates of less than 50%, but many of the study populations included patients with lower-acuity PE. Where a cardiac arrest subgroup was reported, mortality rates of up to 64% were found. In our study, all patients had massive PE and 4/9 presented in cardiac arrest, giving them a higher predicted mortality than other patients with PE.

It is difficult to draw significant conclusions about mortality rates given the small numbers in each group in our study and the possibility of selection bias. However, over the past decade there has been a liberalising of indications for embolectomy to include patients without massive PE, and reported mortality has fallen to under 15%. Given the paucity of prospective trial data, it remains unclear whether these patients could have been managed just as successfully with therapeutic anticoagulation. In our study, resource utilisation with embolectomy was higher than with either anticoagulation or thrombolysis, as evidenced by the longer ICU length of stay and increased duration of mechanical ventilation. Furthermore, haemorrhagic complications associated with embolectomy were greater than with the other therapies. Without clear evidence of a mortality benefit to the patient of embolectomy over heparinisation, it is difficult to justify the additional resource utilisation.

Of patients who had an IVC filter inserted, all but one survived. This is in accordance with the ICOPER registry data, which also noted a survival benefit associated with the use of IVC filters. However, it is important to note that in our patients, IVC filters were placed after the patient had survived the initial PE, had already had primary therapy and had a documented persisting DVT. Hence there is significant selection bias in patients who received an IVC filter, which may have contributed to the outcome. An RCT comparing
vena caval filters and anticoagulation with anticoagulation alone demonstrated a reduction in recurrent PE associated with caval filters but no survival benefit.16 Caval filters are associated with significant complications, including an increased incidence of recurrent DVT, migration of the caval filter, and occlusion of the inferior vena cava.15,25,26 Current guidelines recommend that they be used in cases where there is an absolute contraindication to anticoagulation and a high risk of DVT recurrence.5 Hence, although there is an interesting association with survival, further studies need to be performed to elucidate the role of the caval filter.

A particular strength of our study was that patients with massive PE were clearly identified according to current definitions. This allowed selection of a population of interest, rather than selection by treatment strategy, thus making a more homogenous study group. Our method of searching multiple databases means it is unlikely that any patients with actively managed PE were missed. Being a single-centre study added further homogeneity to the results, notwithstanding the changes in practice over time. On the other hand, as it was a retrospective study, with decisions made by the attending physician on clinical grounds and no unifying protocols in place, selection bias was unavoidable. The relatively small size of the subgroups must be considered when making comparisons between treatment groups. Unidentified confounding factors may also have influenced the outcomes. Furthermore, missing data in medical records may have meant that some patients with massive PE were not identified or that certain data confirming the diagnosis, such as echocardiographic results, were not available.

Our results highlight the significant mortality associated with massive PE and the underlying comorbidities that make therapeutic decisions difficult. We could not demonstrate a mortality benefit with thrombolysis, embolectomy or anticoagulation, although resource utilisation was higher with embolectomy. Certainly patients who received therapeutic anticoagulation alone did not have a worse outcome than other patient groups, and our results would support the use of heparin alone in patients for whom there is a significant contraindication to thrombolysis or surgical pulmonary embolectomy.

Given the lack of evidence to support any particular management strategy in massive PE, and the suggestion from retrospective trials that there is no benefit associated with thrombolysis or embolectomy over anticoagulation alone, a well-designed trial into the optimal therapeutic strategy for massive PE would appear to be warranted. This should, at the least, be a prospective observational trial. A prospective RCT, while theoretically superior, would be difficult to conduct, given the infrequency and urgency of massive PE, but with involvement of multiple centres, an RCT may be possible.

Conclusion

Our study demonstrated no difference between thrombolysis, surgical embolectomy and therapeutic anticoagulation with heparin for the management of massive pulmonary embolism. Although this result differs from expert opinion, it is in accordance with much of the published literature. Further evaluation of the optimal management of massive PE appears warranted.

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* Dr Ramakrishnan sadly passed away during the preparation of this manuscript.

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