In-hospital and long-term outcome after sub-massive and massive pulmonary embolism submitted to thrombolytic therapy

Nicolas Meneveaua*, Liu Pin Mingb, Marie France Séronde a, Nursen Mersina, François Schiele a, Fiona Caulfield a, Yvette Bernard a, Jean-Pierre Bassanda

a Department of Cardiology, University Hospital Jean-Minjoz, Boulevard Fleming, 25030 Besançon Cedex, France
b Department of Cardiology, Second Affiliated Hospital, Sun Yat-sen University, Guangzhou 510120, China

Received 10 March 2003; received in revised form 15 May 2003; accepted 21 May 2003

Background From a registry of 249 confirmed pulmonary embolism (PE) patients submitted to thrombolytic therapy (TT), we analysed predictors of in-hospital course and long-term mortality.

Methods and results The combined clinical end point of in-hospital course associated death, recurrent PE, repeat thrombolysis, surgical embolectomy or bleeding complications. The long-term follow-up included analysis of survival, and occurrence of PE-related events, defined as recurrent deep vein thrombosis, recurrent PE, occurrence of congestive heart failure or change of New York Heart Association functional class to class III or IV in patients who survived the acute phase.

In-hospital clinical course was uneventful in 165 (66.3%) patients. Initial right ventricular (RV) dysfunction was reversible in 80% within 48 h following TT. Initial pulmonary vascular obstruction >70% (RR=5.3 [2.1; 13.6]; P=0.0001); haemodynamic instability at presentation (RR=2.6 [1.1; 6]); persistence of septal paradoxical motion after TT (RR=5.9 [1.4; 25.9]); and insertion of intracaval filter (RR=3.7 [1.4; 9.4]) were independent predictors of poor in-hospital course. Mean follow-up was 5.3±2.6 years. Of the 227 patients alive after the hospital stay, the probability of survival was 92% at 1 year, 79% at 3 years and 56% at 10 years. Multivariate predictors of long-term mortality were age >75 years (RR=2.73 [2.18; 3.21]; P=0.0002), persistence of vascular pulmonary obstruction >30% after thrombolytic treatment (RR=2.22 [1.69; 2.74]; P=0.003), and cancer (RR=2.03 [1.40; 2.65]; P=0.04).

Conclusion The recovery of RV function should be considered as a marker of thrombolysis efficacy, while residual pulmonary vascular obstruction and cancer are independent predictors of long-term mortality. These results advocate the identification of high-risk patients by means of systematic lung-scan and echocardiography pre- and post-thrombolysis, and raise the question of the need for thromboendarterectomy in patients with residual pulmonary vascular obstruction.

© 2003 Published by Elsevier Ltd on behalf of The European Society of Cardiology.

KEYWORDS
Embolism; Thrombolysis; Hypertension; Pulmonary
compensated systemic perfusion and right ventricular (RV) dysfunction. In such patients, thrombolysis accelerates clot lysis and resolution of pulmonary hypertension (PH) as well as right ventricular afterload, when compared with conventional heparin coagulation.

This early improvement might be of importance, since persistence of PH/RV dysfunction weeks after diagnosis of PE has been associated with increased long-term mortality rates. To date however, the identification of predictive factors of short-term clinical outcome in patients with massive PE submitted to thrombolytic therapy has not been specifically undertaken. In addition, the impact of these early haemodynamic and clinical benefits on long-term evolution have not yet been investigated.

Therefore, this study was designed to evaluate the in-hospital course and long-term evolution of patients with massive PE submitted to thrombolytic therapy, and to determine the independent predictors of short and long-term prognosis in these patients.

Methods

Selection of patients

The study population was derived from a single-centre prospective registry of patients with confirmed pulmonary embolism and submitted to a thrombolytic treatment between 1990 and 1999.

The initial assessment included clinical history, routine physical examination, chest X-ray, 12-lead ECG, arterial blood gas analysis and lower limb venous ultrasonography. The diagnosis of PE was based on pulmonary angiogram, ventilation/perfusion scan, or spiral CT scan. From May 1993 onwards, transthoracic echocardiography was systematically performed as soon as PE was diagnosed.

Patients with proven recent PE (symptom onset <15 days) and no contraindication of thrombolytic therapy were included in the registry if they met at least one of the following criteria: (1) cardiogenic shock defined as systolic blood pressure <90 mmHg associated with clinical signs of organ hypoperfusion and hypoxia, (2) syncope, (3) pulmonary vascular obstruction >50%, (4) mean pulmonary artery pressure (MPAP) >20 mmHg by right heart catheterization, (5) ≥1 echocardiographic findings indicating RV dysfunction (RV dilatation, i.e., RV/left ventricular end-diastolic diameter ratio ≥1 in the 4-chamber view, paradoxical septal systolic motion and/or PH defined as a RV/atrial gradient >30 mmHg).

Management strategies and medication

The therapeutic approach was left to the discretion of the attending physician. Three thrombolytic agents were utilized using a total of six different regimens, as previously described elsewhere. Intravenous unfractionated heparin was started at the end of thrombolytic infusion, maintained at a dose of 1000 IU/h and adapted to achieve an activated partial thromboplastin time ratio of two to three times the control value. Until 1992, intracaval devices were implanted in case of contraindication to oral anticoagulant, extensive proximal venous thrombosis or surgical embolectomy. From 1992 onwards, indications for intracaval devices were restricted to patients with absolute contraindication to oral anticoagulant, due to the increased risk of bleeding linked to the insertion of these devices. Oral anticoagulant therapy was introduced within 3–5 days and was continued for ≥6 months, adjusted to maintain the international normalized ratio between 2 and 3.

In hospital Course

Adverse events such as death, recurrent PE, repeat thrombolysis, surgical embolectomy and bleeding complications were noted throughout the hospital stay. From 1993, repeat echocardiographic examination was systematically performed 48 h after thrombolytic therapy and RV dysfunction criteria were recorded. Similarly, perfusion lung scans were taken within 6 to 8 days after the onset of treatment. Six-view ventilation and perfusion lung scans were obtained in a single session with a high resolution, low energy, large-field camera (Sophy Camera DS7). Perfusion impairment was graded as to the proportion of lung not perfused, according to a segmental method that account for all views.

Long-term follow-up

Follow-up data were obtained either during hospital readmission, or during patient visits to the department, or from a standardized questionnaire sent to the attending physicians and/or cardiologists. During data collection, particular emphasis was paid to clinical events including death, cause of death, recurrent phlebitis, recurrent PE, development of congestive heart failure or change of New York Heart Association (NYHA) functional class to class III or IV. Hospital records, and death certificates of patients who died during the follow-up period were also reviewed. Follow-up was concluded in October 1999, and patients were considered lost to follow-up if their last contact was before October 1998.

Definition of clinical end-points

The clinical end-point of in-hospital course was a combined end-point including death, recurrent PE, repeat thrombolysis, surgical embolectomy or bleeding complications. Major bleeding complications were prospectively defined as any bleeding event that required blood transfusion, surgical control, discontinuation of thrombolytic or anticoagulant treatment; haemorrhagic stroke confirmed by computed tomography or autopsy; or any bleeding causing death or a fall of 15% in haematocrit. Other important bleedings, defined as a fall of 10% in haematocrit were also recorded. Patients with symptoms suggesting PE and with new perfusion defects on the lung scan or pulmonary angiogram were interpreted as having recurrent PE.

The long-term follow-up included analysis of survival, and occurrence of PE-related events, defined as recurrent deep vein thrombosis, recurrent pulmonary embolism, occurrence of congestive heart failure or change of NYHA functional class to class III or IV.

Statistical analysis

Continuous variables are expressed as mean±SD; categorical variables, as percent. Student’s t-test and [chi]2 analysis were carried out for comparison of continuous and categorical variables, respectively. Pairwise t test was used to compare baseline results with those obtained 24–48 h after thrombolysis. A P value <0.05 was considered significant. Analysis was performed with BMDP statistical software package (BMDP Statistical Software, Inc. Los Angeles, California).

In the uni- and multivariate analysis carried out to identify predictive factors of in-hospital course and long-term follow-up,
the statistical analysis took into account only those patients who were consecutively included in the registry from 1993 onwards, as they were subject to the new management strategy of systematic echocardiography and lung scan pre- and post-thrombolysis (n=183 patients). In-hospital and late follow-up outcomes were independently analysed. Continuous variables were divided into subgroups with clinically chosen cutoff points. Predictors of in-hospital course were determined by uni- and multivariate logistic regression analysis. Twenty-two variables listed in Table 4 were tested to determine significant univariate correlates of combined major adverse events. Univariate correlates with a P value <0.10 were considered significant and were included in the multiple stepwise logistic regression analysis to determine independent predictors of combined in-hospital major adverse events.

Analysis of the predictive factors of long-term mortality in patients who survived the acute phase was completed by the Cox proportional hazards model. Univariate analysis was performed using a log-rank test on the 22 variables listed in Table 4 plus the duration of oral anticoagulant therapy. Significant explanatory variables with P<0.10 were included in the Cox multivariate model, using a stepwise procedure. The 95% confidence interval for relative risk was derived from the natural logarithm of (coefficient±1.96 times the standard error). Cumulative survival curves of patients with and without residual pulmonary vascular obstruction were generated by the Kaplan–Meier method and compared by the log-rank test.

Results

From January 1990 to October 1999, 1034 consecutive patients were referred to the Cardiology Department with confirmed PE, of whom 249 (24%) were treated with thrombolytic therapy.

Clinical findings on admission

The study population was made up of 140 females (56%) and 109 males (44%), with a mean age of 66±14 years (range 17–92 years). PE was diagnosed by pulmonary angiograms in 178 (72%) patients, high probability lung scans in 66 (27%) patients, and spiral computed tomography scans in 38 (15%) patients. Of these, all but three patients who underwent spiral CT scan were systematically submitted to perfusion lung scan. The clinical characteristics of patients at admission are reported in Table 1.

Nine (4%) patients presented with initial shock, 57 (23%) with syncope, and 18 (9%) with arterial hypotension. A total of 66 (27%) patients initially presented with at least one of the above signs. Tachycardia, defined as heart rate >100 beats/min, and severe hypoxaemia defined as partial arterial oxygen pressure <55 mmHg without oxygen therapy, were observed in 134 (54%) and in 65 (26%) patients respectively. Cancer and previous deep-vein thrombosis or PE were the most common pre-existing disorders.

Initial severity of PE (Table 2)

The severity of pulmonary vascular obstruction, available in 98% of patients, was 64±14%. Furthermore, mean pulmonary artery pressure was 35±12 mmHg in the 62% of patients who underwent right heart catheterisation. Transthoracic echocardiographic examination revealed the presence of RV dysfunction in 157 out of 183 patients (86%). RV dilatation was the most common sign of RV overload. Pulmonary hypertension was diagnosed in 136 (74%) patients in which the mean systolic pressure was 56±13 mmHg, corresponding to a tricuspid regurgitant jet velocity of 3.6±1.2 m s⁻¹.

In-hospital course

The mean duration of hospital stay was 11±4 days. Of the 249 patients, 68 (27%) received rt-PA (53 as a 2-h infusion; 15 as a 15-min infusion), 179 (72%) patients were treated with streptokinase (127 as a 12-24 h infusion; 52 as a 2-h infusion), and two patients with urokinase (1 as a 12–24 h infusion; 1 as a 20-min infusion). The thrombolytic therapy was started less than 5 days after onset of symptoms in 127 (51%) patients and within 5 to 15 days after onset of symptoms in the remaining 122 (49%) patients.

The in-hospital clinical course was uneventful in 165 (66%) patients. Twenty-two (8.8%) patients died, of whom six died from major bleeding, one from cancer, and 15 from the pulmonary embolism process (four patients from refractory shock and 11 patients from recurrent PE). A total of 19 (7.6%) had fatal or non-fatal recurrent PE. Over the first 48 h, heart rate dropped from 101±20 to 79±14 beats/min while partial arterial oxygen pressure increased from 56±11 to 72±13 mmHg. Right ventricular dysfunction and vascular pulmonary obstruction improved significantly following thrombolytic therapy (Table 3). Mean systolic pulmonary pressure assessed by echocardiography decreased by 34% over the first 2 days (56±13 mmHg vs 37±10 mmHg; P=10⁻³). In patients who had echocardiography both pre- and post-thrombolysis, initial RV dysfunction was reversible in 125 (80%) within 48 h following thrombolytic therapy. Repeat lung scan performed at 6–8 days showed a significant 45% improvement in vascular pulmonary perfusion.

<table>
<thead>
<tr>
<th>Table 1 Patient characteristics at diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Sex (Female/Male)</td>
</tr>
<tr>
<td>Age (Years)</td>
</tr>
<tr>
<td>Shock</td>
</tr>
<tr>
<td>Syncope</td>
</tr>
<tr>
<td>Systolic blood pressure ≤90 mmHg</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
</tr>
<tr>
<td>PaO₂ (mmHg)</td>
</tr>
<tr>
<td>ECG with RV overload</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
</tr>
<tr>
<td>History of thrombo-embolic disease</td>
</tr>
<tr>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
</tr>
<tr>
<td>Cancer</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>n=183</td>
</tr>
</tbody>
</table>

*PaO₂=partial arterial oxygen pressure without oxygen therapy.
Lack of clinical and/or vascular pulmonary obstruction improvement led to repeat thrombolysis and surgical embolectomy in 20 and 13 patients, respectively. Partial interruption of the inferior vena cava was carried out in 51 (20%) patients.

Forty-three (17.3%) patients suffered from bleeding complications. Major bleedings occurred in 24 (9.6%) patients (six fatal, of which three hemorrhagic strokes) and important bleedings occurred in 19 (7.6%). The majority of major bleedings were related to an early invasive procedure (pulmonary angiography (11 patients), insertion of intracaval device (five patients)). Surgical control of haematoma and blood transfusion were needed in respectively six and 18 patients. Other important bleedings were related to haematoma at puncture sites (13 patients), haematuria (3 patients), and gastrointestinal bleeding (three patients).

By univariate analysis, seven variables associated with short-term clinical adverse outcome were identified (Table 4). Cancer, haemodynamic instability (shock or low blood pressure at admission, syncope), presence of deep vein thrombosis, and vascular pulmonary obstruction >70% were pre-treatment characteristics associated with adverse events. Heart rate >100 bpm, paradoxical septal systolic motion and insertion of intracaval device were post-treatment characteristics related to adverse clinical events. Deep vein thrombosis was inversely associated with in-hospital adverse events. Initial haemodynamic instability, pulmonary vascular obstruction >70% and insertion of intracaval device were independent predictors of poor in-hospital evolution in multivariate analysis (Table 4).

### Long-term Evolution

Patients who died during the in-hospital phase were excluded from the long-term analysis. Mean follow-up was 5.3±2.6 years (range [2.6–10.5]) and follow-up was complete for 98% of patients. Of the 227 patients alive after the hospital stay, 70 (31%) died during the follow-up. The cause of death were cancer (22 (31%)), heart failure (13 (18%)) recurrent PE (13 (18%)), stroke (5 (7%)), postoperative complications (5 (7%)), acute myocardial infarction (3 (4%)), pneumonia (1 (2%)), Alzheimer’s disease (1 (2%)), renal failure (1 (2%)), bleeding events (1 (2%)) and uncertain (5 (7%)). In the entire population of 227 patients the probability of survival was 95% at 3 months, 92% at 1 year, 79% at 3 years and 56% at 10 years (Fig. 1).

The predictive analysis of long-term mortality in patients who survived the acute phase was performed using the variables listed in Table 4, plus duration of oral anticoagulant therapy (6 months or permanent). The cut off value of post-thrombolysis systolic PH used in the predictive analysis of long-term PE-related events was 40 mmHg. Univariate predictors of long-term adverse events were age >75 (P=0.0003), PaO2 <55 mmHg (P=0.04), cancer (P=0.08), systolic blood pressure ≤90 mmHg, (P=0.08), as pre-thrombolysis variables; and residual vascular pulmonary obstruction >30% (P=0.004), and vena cava filter insertion (P=0.02) as post-thrombolysis variables. At multivariate analysis, age >75 years (RR=2.73 [2.18; 3.21]; P=0.0002), persistence of vascular pulmonary obstruction >30% after thrombolytic treatment (RR=2.22 [1.69; 2.74]; P=0.003), and cancer (RR=2.03 [1.40; 2.65]; P=0.04), were identified as independent predictors of long-term mortality (Table 5). The difference in survival between patients with and

---

**Table 2** Pulmonary embolism severity

<table>
<thead>
<tr>
<th>Echocardiography (183/249 patients)</th>
<th>Baseline</th>
<th>24–48 h after thrombolysis</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV dilatation</td>
<td>151 (83%)</td>
<td>32 (18%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Intracardiac thrombus</td>
<td>8 (4%)</td>
<td>3 (2%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Paradoxical septal systolic motion</td>
<td>94 (51%)</td>
<td>15 (8%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Systolic pulmonary pressure (&gt;30 mmHg)</td>
<td>136 (74%)</td>
<td>37 (20%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥1 of the above</td>
<td>157 (86%)</td>
<td>32 (17%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ventilation/Perfusion Lung Scan (225/249 patients)</th>
<th>Baseline</th>
<th>6–8 days after thrombolysis</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean vascular pulmonary obstruction</td>
<td>64±14%</td>
<td>29±13%</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

**Table 3** In-hospital clinical course

<table>
<thead>
<tr>
<th></th>
<th>n=249</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital uneventful clinical course</td>
<td>165 (66%)</td>
</tr>
<tr>
<td>Death</td>
<td>22 (8.8%)</td>
</tr>
<tr>
<td>Refractory shock</td>
<td>4</td>
</tr>
<tr>
<td>Recurrent PE</td>
<td>11</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>6</td>
</tr>
<tr>
<td>Cancer</td>
<td>1</td>
</tr>
<tr>
<td>Recurrent PE (fatal and non fatal)</td>
<td>19 (7.6%)</td>
</tr>
<tr>
<td>Repeat thrombolysis</td>
<td>20 (8%)</td>
</tr>
<tr>
<td>Surgical embolectomy</td>
<td>13 (5%)</td>
</tr>
<tr>
<td>Cava filter insertion</td>
<td>51 (20%)</td>
</tr>
<tr>
<td>Bleeding complications (total)</td>
<td>43 (17.3%)</td>
</tr>
<tr>
<td>Major bleedings</td>
<td>24 (9.6%)</td>
</tr>
<tr>
<td>Cerebral</td>
<td>3</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>3</td>
</tr>
<tr>
<td>Hematoma (vascular access)</td>
<td>16</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
</tr>
</tbody>
</table>

1450 N. Meneveau et al.
without residual pulmonary vascular obstruction became apparent immediately after hospital discharge and worsened steadily thereafter (Fig. 2).

Eighty-two (36%) patients experienced PE-related events during the follow up period and had a worse long-term prognosis, with a significant global
over-mortality as compared to the rest of the study population (37 deaths out of 82 patients with PE-related events (45%) vs 33 deaths out of 145 patients without PE-related events (23%); \( P=0.01 \)) (Table 6).

**Discussion**

This study is the first study to evaluate the short- and long-term effects of thrombolytic therapy in a large cohort of patients with massive PE. The study was not designed to identify those patients in whom thrombolytic treatment has a favourable risk-to-benefit ratio, and thus the indications for thrombolysis, particularly in submassive PE, remain to be defined.

**Early clinical course**

The overall in-hospital mortality rate observed in this study (8.8%) is comparable to that reported by Carson et al. and by the ICOPER investigators (9.5% and 11.4% at
Late results of thrombolytic therapy in massive PE

Thrombolysis was found to improve pulmonary capillary blood flow volume at 1 year and to induce a better pulmonary vascular response to exercise at 7 years when compared with heparin in a small ancillary study. To date, no study has specifically assessed the clinical evolution of massive PE beyond one year after thrombotic therapy. The mortality rate over the first year following PE usually ranged between 17 and 24% and was related to underlying diseases. In patients who survived an episode of acute PE, Paraskos et al. reported a mortality rate of 32% at 29 months, which was mainly linked to the presence of pre-existing cardiac disease. In our study, the main cause of death was cancer (31%), whereas heart failure and recurrent PE were each responsible for 18% of deaths.

This study is the first report of long-term mortality in patients with massive and submassive PE submitted to thrombolysis and who survived the acute phase. Our findings made it possible to identify clearly the patients who were most likely to die during the years following the thrombo-embolic event; namely older patients, and those with persistent pulmonary obstruction after thrombolytic therapy, as well as patients with severe underlying disease such as cancer. Previous studies have shown that approximately 15 to 25% of patients show only partial resolution of pulmonary vascular obstruction and that the persistence of PH after embolization is associated with increased mortality rates. In addition, long-term survival is markedly related to persistent PH/RV dysfunction several weeks after diagnosis of acute PE. One of the independent prognostic factors of long-term evolution that we identified was related to the residual clot burden due to incomplete pulmonary revascularization after thrombolytic therapy. These data are in agreement with those recently reported by Ribeiro et al. Whether patients with persistent pulmonary vascular obstruction later develop chronic thromboembolic pulmonary hypertension is still unclear and would require additional investigation. It has previously been hypothesized that chronic thromboembolic pulmonary hypertension is rare among patients with prior pulmonary embolism. However, our findings suggest that these figures could be underestimated, and would encourage careful follow-up of patients with residual pulmonary vascular obstruction in order to identify suitable candidates for pulmonary thromboendarterectomy.

Our results advocate the identification of high risk patients by means of systematic lung-scan and echocardiography before discharge from the hospital.

Study limitations

The long-term follow-up did not include systematic lung-scan and echocardiography, so it was thus impossible to diagnose chronic cor pulmonale. However, this diagnosis is reported in a very limited number of cases, although recent studies suggest that its prevalence may be underestimated. The evaluation of prognostic factors for short and long-term outcome only concerned the 183 consecutive patients included in the register from 1993 onwards, and who had been submitted to systematic repeat lung scan and echocardiography. Nonetheless, the incidence of major adverse events in this sub-group did not significantly differ from that of the total population (P=0.88).

Furthermore, the fact that six different thrombolysis regimens were used is another limitation of the study, because the clinical and haemodynamic benefits of the various thrombolytic agents and regimens are not strictly identical.

Conclusion

The initial severity of massive and sub-massive PE submitted to thrombolysis predicts in-hospital evolution. The recovery of RV function should be considered as a marker of thrombolysis efficacy, as well as a predictor of in-hospital course in these patients. As regards long-term follow-up, this study identified residual pulmonary vascular obstruction and cancer as independent predictors of long-term mortality. These results advocate the identification of high risk patients by means of systematic lung-scan and echocardiography pre- and post-thrombolysis and raise the question of the need for
thromboendarterectomy in patients with residual pulmonary vascular obstruction after thrombolytic therapy for massive or sub-massive PE.

References