Massive Pulmonary Embolism

Nils Kucher, MD; Elisa Rossi, BS; Marisa De Rosa, PhD; Samuel Z. Goldhaber, MD

Background—Acute massive pulmonary embolism (PE) carries an exceptionally high mortality rate. We explored how often adjunctive therapies, particularly thrombolysis and inferior vena caval (IVC) filter placement, were performed and how these therapies affected the clinical outcome of patients with massive PE.

Methods and Results—Among 2392 patients with acute PE and known systolic arterial blood pressure at presentation, from the International Cooperative Pulmonary Embolism Registry (ICOPER), 108 (4.5%) had massive PE, defined as a systolic arterial pressure <90 mm Hg, and 2284 (95.5%) had non–massive PE with a systolic arterial pressure ≥90 mm Hg. PE was first diagnosed at autopsy in 16 patients (15%) with massive PE and in 29 patients (1%) with non–massive PE (P<0.001). The 90-day mortality rates were 52.4% (95% CI, 43.3% to 62.1%) and 14.7% (95% CI, 13.3% to 16.2%), respectively. In-hospital bleeding complications occurred in 17.6% versus 9.7% and recurrent PE within 90 days in 12.6% and 7.6%, respectively (P<0.001). In patients with massive PE, thrombolysis, surgical embolectomy, or catheter embolectomy were withheld in 73 (68%). Thrombolysis was performed in 33 patients, surgical embolectomy in 3, and catheter embolectomy in 1. Thrombolytic therapy did not reduce 90-day mortality (thrombolysis, 46.3%; 95% CI, 31.0% to 64.8%; no thrombolysis, 55.1%; 95% CI, 44.3% to 66.7%; hazard ratio, 0.79; 95% CI, 0.44 to 1.43). Recurrent PE rates at 90 days were similar in patients with and without thrombolytic therapy (12% for both; P=0.99). None of the 11 patients who received an IVC filter developed recurrent PE within 90 days, and 10 (90.9%) survived at least 90 days. IVC filters were associated with a reduction in 90-day mortality (hazard ratio, 0.12; 95% CI, 0.02 to 0.85).

Conclusions—In ICOPER, two thirds of the patients with massive PE did not receive thrombolysis or embolectomy. Counterintuitively, thrombolysis did not reduce mortality or recurrent PE at 90 days. The observed reduction in mortality from IVC filters requires further investigation. (Circulation. 2006;113:577-582.)

Key Words: embolism ■ mortality ■ thrombolysis

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Methods

ICOPER enrolled 2454 consecutive patients with acute PE from 52 institutions in 7 countries, from January 1995 through November 1996. In the present analysis, we evaluated 2392 patients with acute PE and known systolic arterial pressure at presentation. One hundred eight (4.5%) had massive PE, defined as a systolic arterial pressure <90 mm Hg, and 2284 (95.5%) had non–massive PE with a systolic arterial pressure ≥90 mm Hg. The remaining 62 patients were excluded because of unknown systolic arterial pressure at presentation.

Inclusion criteria for ICOPER were acute PE diagnosed by the attending physician within 31 days of symptom onset or major PE first discovered by autopsy. There were no exclusion criteria. The diagnosis of PE was accepted without independent review if confirmed by high-probability lung scan, pulmonary angiography, venous ultrasound of the leg veins in the presence of a high clinical suspicion of PE, or necropsy. The diagnosis of concomitant deep vein thrombosis was accepted when objectively confirmed by phlebography or venous ultrasound. Echocardiography was recom-
thrombolysis was administered in 33 patients, surgical embolec-
tomy was withheld in 73 patients (68%). Throm-
bolysis was administered in 33 patients, surgical embolec-
tomy in 3, and catheter embolectomy in 1. Age (64±13
versus 64±19 years) and sex (39% versus 41% men) were
similar between the patients who did and did not receive
thrombolysis, respectively (Table 3). Among the 61 patients
who underwent baseline echocardiography, right ventricular
hypokinesis was more common (85%) among those who
received thrombolysis compared with the no-thrombolysis
group (44%) (P=0.001). In patients who received
thrombolysis, cancer was less often present (6% versus 28%),
and prior deep vein thrombosis (38% versus 6%) or prior PE
(13% versus none) was more often present.

Thrombolytic therapy did not reduce 90-day mortality
(HR, 0.79; 95% CI, 0.44 to 1.43; P=0.44). The 90-day
mortality rates were 46.3% (95% CI, 31.0% to 64.8%) in
patients with thrombolytic therapy and 55.1% (95% CI,
44.3% to 66.7%) in patients without thrombolysis (Figure 2).

In-hospital bleeding complications occurred often in both
the thrombolysis and no-thrombolysis groups (24% and
15%), and recurrent PE at 90 days was equal (12% for both).
Recurrent PE was a predictor of 90-day mortality both in
patients with thrombolytic therapy (HR, 6.71; 95% CI, 1.81
to 24.81; P=0.004) and in those without thrombolytic ther-
apy (HR, 2.39; 95% CI, 1.09 to 5.21; P=0.029).

The 11 massive PE patients who received an IVC filter
were younger than the massive PE patients without IVC filter
placement (Table 4). None of the patients who received an
IVC filter developed recurrent PE within 90 days, and 10
(90.9%) survived 90 days (Figure 3). In contrast, 13 of 97
patients without an IVC filter (13.4%) developed recurrent
PE within 90 days, and 55 (56.7%) of the 97 survived 90
days. IVC filters were associated with a reduction in 90-day
mortality (HR, 0.12; 95% CI, 0.02 to 0.85; P=0.002).

In the patients with non–massive PE, 90-day survival rates
were 79.3% (95% CI, 74.3% to 84.1%) in patients with
thrombolysis and 86.1% (95% CI, 84.5% to 87.5%) in
patients without thrombolysis (HR, 1.56; 95% CI, 1.16 to
2.10; P=0.003); 90-day survival rates were 79.1% (95% CI,
73.2% to 83.9%) in patients with an IVC filter and 86.0% (95% CI,
84.5% to 87.5%) in those without an IVC filter (HR,
1.50; 95% CI, 1.10 to 2.04; P=0.009).

Discussion

We found that certain comorbidities were associated with
massive rather than non–massive PE: congestive heart failure,
renal dysfunction, and reduced left ventricular systolic ejec-
tion fraction. One third of the massive PE patients had no
echocardiographic right ventricular hypokinesis; at least in
some of these patients, cardiopulmonary comorbidities may
have been the main cause of hemodynamic instability. Mas-
sive PE was associated more often with right heart thrombi
(10%) than non–massive PE (4%). This finding is important
because echocardiographic evidence of right heart thrombi
in the setting of massive PE may change the treatment plan from
thrombolysis to surgical embolectomy.

Since the conclusion of ICOPER, chest CT has virtually
replaced lung scanning for diagnosing PE at most hospitals,7
resulting in more rapid and accurate diagnosis. Rapid diag-
nosis of massive PE is crucial to initiate potentially life-
saving therapy. Chest CT is not only useful to diagnose PE

Adjunctive Therapies

Thrombolysis, surgical embolectomy, or percutaneous cath-
er embolectomy was withheld in 73 patients (68%). Throm-
bolysis was administered in 33 patients, surgical embolec-

Results

Comparison of Patients With Massive and
Non–Massive PE

Age (64±17 versus 62±17 years) and gender (41% versus
45% men) were similar in patients with massive and non–massive PE, respectively (Table 1). PE was first diagnosed at
autopsy in 16 (15%) of the patients with massive PE and in 29
(1%) of the patients with non–massive PE (P<0.001).

Among the 1096 patients who underwent baseline echocar-
diography within 24 hours of PE diagnosis, right ventricular
hypokinesis was present in 62% of the patients with massive PE compared with 39% of the patients with non–massive PE.
Right heart thrombi were more often found in patients with
massive PE (10% versus 4%). Patients with massive PE more
often had congestive heart failure (22% versus 10%), reduced
left ventricular ejection fraction of <40% (15% versus 6%),
and renal dysfunction (15% versus 5%). Cancer rates were
similar in both groups (21% versus 22%). Concomitant deep
vein thrombosis was less often diagnosed in patients with
massive PE (32% versus 50%).

The 90-day mortality rates were 52.4% (95% CI, 43.3% to
62.1%) and 14.7% (95% CI, 13.3% to 16.2%) in patients with
massive and non–massive PE, respectively (Figure 1). PE
was the cause of death in 62.5% of the patients with massive
PE and in 34.0% of the patients with non–massive PE (Table
2). In-hospital bleeding complications occurred in 17.6%
versus 9.7%, and recurrent PE was detected within 90 days in
12.6% and 7.6%, respectively, in patients with massive
versus non–massive PE (P<0.001).

The 11 massive PE patients who received an IVC filter
development PE within 90 days, and 10
(90.9%) survived 90 days (Figure 3). In contrast, 13 of 97
patients without an IVC filter (13.4%) developed recurrent
PE within 90 days, and 55 (56.7%) of the 97 survived 90
days. IVC filters were associated with a reduction in 90-day
mortality (HR, 0.12; 95% CI, 0.02 to 0.85; P=0.002).

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84.5% to 87.5%) in those without an IVC filter (HR,
1.50; 95% CI, 1.10 to 2.04; P=0.009).

Discussion

We found that certain comorbidities were associated with
massive rather than non–massive PE: congestive heart failure,
renal dysfunction, and reduced left ventricular systolic ejec-
tion fraction. One third of the massive PE patients had no
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nosis of massive PE is crucial to initiate potentially life-
saving therapy. Chest CT is not only useful to diagnose PE

adjunctive therapies were not centrally adjudicated. Right ventricular hy-
plasia was defined as moderate or severe systolic hypokinesis of the
right ventricular free wall by qualitative assessment. Left ventricular ejection fraction was obtained from the baseline echo-
cardiogram. ICOPER did not issue guidelines for the management of
the registered patients. The administration of anticoagulation or
thrombolysis and the use of embolectomy and placement of IVC
filters were decided entirely by site physicians. Site investigators
performed 90-day follow-up by telephone interview, and follow-up
was completed in 2343 (98%) of the 2392 patients included in this
analysis. Completed case report forms were sent to and analyzed by
the Data Coordinating Center, CINECA, Bologna, Italy. Institutional
ethics committee approval was obtained from the participating
hospitals.

We used the Mann-Whitney test for comparisons of continuous
variables between patients with massive and non–massive PE and the
χ² test or Fisher exact test for comparisons of nominal variables.
These tests were also used to explore differences between the
patients with massive PE who did and did not receive systemic
intravenous thrombolysis. The Kaplan-Meier estimator and log-rank
test were used to estimate the cumulative probability of overall and
cardiovascular death at 90 days in the groups. Cardiovascular
mortality was defined as death from PE, acute myocardial infarction,
stroke, or sudden cardiac death. The Cox proportional hazard model
was used to calculate the univariate hazard ratio (HR) of clinical
variables for predicting 90-day mortality in the defined groups. All
reported probability values are 2 tailed.
and assess clot burden but helps to identify patients with right ventricular enlargement who are at increased risk of early death.8,9 We were surprised to find that two thirds of the patients with massive PE did not receive any adjunctive therapy such as thrombolysis or embolectomy. Unfortunately, we were not able to explore the reasons for withholding thrombolysis or embolectomy. The 15% missed massive PEs can only partly explain the omission of therapy. Therefore, it remains hypothetical whether thrombolysis or embolectomy was actively withheld or simply not considered. It is likely that neither surgical embolectomy nor percutaneous catheter thrombectomy was available in most of the participating hospitals. However, this does not explain the omission of thrombolysis.

At first glance, it seemed surprising and counterintuitive that thrombolysis did not improve survival. That thrombolysis patients more frequently than no-thrombolysis patients had right ventricular hypokinosis raises the possibility that these patients had more severe PE. However, in some patients thrombolysis was probably contraindicated because of severe comorbidities despite massive PE. Because most deaths after thrombolysis occurred in the first few days, we hypothesize that many of the patients had suffered irreversible cardiogenic shock and multisystem organ failure due to prolonged systemic arterial hypotension and that thrombolysis was administered too late. We recognize that no definite conclusion about the efficacy of thrombolysis in massive PE can be drawn from the ICOPER because (1) the

### TABLE 1. Patient Characteristics (n=2392)

<table>
<thead>
<tr>
<th></th>
<th>Massive PE (n=108)</th>
<th>Non-Massive PE (n=2284)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SD, y</td>
<td>64±17</td>
<td>62±17</td>
<td>0.12</td>
</tr>
<tr>
<td>Age &gt;70 y</td>
<td>43 (40)</td>
<td>818 (36)</td>
<td>0.40</td>
</tr>
<tr>
<td>Men</td>
<td>44 (41)</td>
<td>1024 (45)</td>
<td>0.40</td>
</tr>
<tr>
<td>Systolic pressure, mean±SD, mm Hg</td>
<td>75±10</td>
<td>131±23</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate, mean±SD, bpm</td>
<td>117±28</td>
<td>98±21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Days from symptom onset to diagnosis, mean±SD</td>
<td>(1.2±2.1)</td>
<td>(4.1±5.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chest pain</td>
<td>41 (40)</td>
<td>1127 (50)</td>
<td>0.06</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>86 (81)</td>
<td>1876 (82)</td>
<td>0.77</td>
</tr>
<tr>
<td>Syncope</td>
<td>41 (39)</td>
<td>271 (12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cough</td>
<td>10 (9)</td>
<td>483 (21)</td>
<td>0.003</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>2 (2)</td>
<td>160 (7)</td>
<td>0.040</td>
</tr>
<tr>
<td>Right ventricular hypokinesis</td>
<td>38/61 (62)</td>
<td>405/1035 (39)</td>
<td>0.001</td>
</tr>
<tr>
<td>Right heart thrombus</td>
<td>6/62 (10)</td>
<td>44/1052 (4)</td>
<td>0.042</td>
</tr>
<tr>
<td>LV ejection fraction &lt;40%</td>
<td>13/88 (15)</td>
<td>104/1777 (6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Concomitant deep vein thrombosis</td>
<td>34/105 (32)</td>
<td>1150/2276 (50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cancer</td>
<td>23 (21)</td>
<td>510 (22)</td>
<td>0.79</td>
</tr>
<tr>
<td>Ongoing cancer chemotherapy</td>
<td>7 (7)</td>
<td>122 (5)</td>
<td>0.60</td>
</tr>
<tr>
<td>Prior deep vein thrombosis</td>
<td>16 (16)</td>
<td>468 (21)</td>
<td>0.19</td>
</tr>
<tr>
<td>Prior PE</td>
<td>4 (4)</td>
<td>207 (9)</td>
<td>0.08</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>20 (19)</td>
<td>277 (12)</td>
<td>0.050</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>23 (22)</td>
<td>230 (10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Trauma within 2 mo</td>
<td>15 (14)</td>
<td>251 (11)</td>
<td>0.35</td>
</tr>
<tr>
<td>Creatinine &gt;2.0 mg/dL</td>
<td>16 (15)</td>
<td>107 (5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>33 (36)</td>
<td>266 (12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heparin*</td>
<td>102 (94)</td>
<td>2,208 (97)</td>
<td>0.21</td>
</tr>
<tr>
<td>Vitamin K antagonist</td>
<td>57 (53)</td>
<td>1,779 (78)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IVC filter</td>
<td>11 (12)</td>
<td>227 (10)</td>
<td>0.59</td>
</tr>
<tr>
<td>Catheter thrombectomy</td>
<td>1 (1)†</td>
<td>14 (&lt;1)</td>
<td>0.50</td>
</tr>
<tr>
<td>Surgical embolectomy</td>
<td>3 (3)‡</td>
<td>11 (&lt;1)</td>
<td>0.02</td>
</tr>
<tr>
<td>No reperfusion therapy</td>
<td>73 (68)</td>
<td>1999 (88)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are numbers of patients with percentages in parentheses unless otherwise specified. LV indicates left ventricular.

*Intravenous or subcutaneous unfractionated heparin or subcutaneous low-molecular-weight heparin.

†One patient underwent both catheter embolectomy and thrombolysis.

‡One patient underwent surgical embolectomy for failed thrombolysis.
patients with and without thrombolysis may not have been comparable because of the nonrandomized design and (2) the relatively small number of patients yielded wide CIs of the mortality estimates.

Patients in shock because of acute myocardial infarction do poorly with thrombolysis alone. To maximize the likelihood of survival, they usually require mechanical intervention with insertion of an intra-aortic balloon pump followed by percutaneous coronary intervention or coronary artery bypass grafting.10,11 By analogy, thrombolysis alone might fail to rescue a substantial proportion of patients with massive PE, even though the Food and Drug Administration has approved thrombolysis for massive PE. Their survival may depend on rapid transfer to a specialized vascular center skilled in surgical or catheter embolectomy. This strategy of rapid referral to specialty hospitals is often used to manage complicated acute myocardial infarction or trauma patients.

With a closely coordinated multidisciplinary PE management program, 1-year survival after surgical embolectomy can be as high as 86%.12 In 35 (74%) of 47 massive PE patients at Brigham and Women’s Hospital, surgical embolectomy was performed before the development of decompen-sated cardiogenic shock.13 Catheter thrombectomy is especially useful in the presence of an increased bleeding risk or if surgical embolectomy is not available or feasible.1 Since the introduction of novel percutaneous interventional thrombectomy devices, such as the Aspirex PE catheter thrombectomy device (Straub Medical)14 or the Angiojet Xpeedior device (Possis),15 the spectrum of interventional approaches to treat massive PE has broadened. The Food and Drug Administration has assigned Humanitarian Use Device status for the Aspirex PE catheter device to treat patients with massive PE in whom thrombolysis is contraindicated.

In ICOPER patients with massive PE, IVC filters appeared to reduce recurrent PE and mortality at 90 days. These findings should be interpreted with caution because of the small percentage of patients (10%) who received an IVC filter.
filter. Although we found no differences in comorbidities except younger age in patients who received an IVC filter, selection bias is likely and makes it difficult to compare the outcome of the filter and no-filter patients. IVC filter placement has been found to reduce recurrent PE but not mortality in patients with non–massive PE. Further studies should be performed before a definitive recommendation is made. Since the conclusion of ICOPER, the use of IVC filters in patients with venous thromboembolism has increased substantially.

In conclusion, the principal findings of this ICOPER analysis of massive PE are that (1) thrombolysis or embolectomy was withheld in two thirds of the patients and (2) thrombolysis did not appear to reduce mortality. These findings imply that there is a need for improved multidisciplinary collaboration to optimize the in-hospital management of patients with acute massive PE, involving vascular medicine specialists, intensive care or emergency medicine specialists, interventional cardiologists/radiologists, and cardiovascular surgeons.

TABLE 4. Characteristics of Massive PE Patients With and Without IVC Filter

<table>
<thead>
<tr>
<th></th>
<th>IVC Filter (n=11)</th>
<th>No IVC Filter (n=97)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SD, y</td>
<td>50±15</td>
<td>66±17</td>
<td>0.003</td>
</tr>
<tr>
<td>Age &gt;70 y</td>
<td>1 (9)</td>
<td>45 (46)</td>
<td>0.023</td>
</tr>
<tr>
<td>Men</td>
<td>8 (73)</td>
<td>36 (37)</td>
<td>0.048</td>
</tr>
<tr>
<td>Systolic pressure, mean±SD, mm Hg</td>
<td>81±2</td>
<td>75±10</td>
<td>0.006</td>
</tr>
<tr>
<td>Heart rate, mean±SD, bpm</td>
<td>138±33</td>
<td>115±26</td>
<td>0.01</td>
</tr>
<tr>
<td>Right ventricular hypokinesis</td>
<td>3/4 (75)</td>
<td>35/57 (61)</td>
<td>1.00</td>
</tr>
<tr>
<td>Right heart thrombus</td>
<td>1/4 (25)</td>
<td>5/58 (9)</td>
<td>0.34</td>
</tr>
<tr>
<td>LV ejection fraction &lt;40%</td>
<td>1/8 (12)</td>
<td>12/80 (12)</td>
<td>1.00</td>
</tr>
<tr>
<td>Concomitant deep vein thrombosis</td>
<td>7 (64)</td>
<td>27 (29)</td>
<td>0.36</td>
</tr>
<tr>
<td>Cancer</td>
<td>4 (36)</td>
<td>19 (20)</td>
<td>0.24</td>
</tr>
<tr>
<td>Prior deep vein thrombosis</td>
<td>2 (18)</td>
<td>14 (15)</td>
<td>0.68</td>
</tr>
<tr>
<td>Prior PE</td>
<td>1 (9)</td>
<td>3 (3)</td>
<td>0.38</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>2 (18)</td>
<td>18 (19)</td>
<td>1.00</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1 (9)</td>
<td>22 (23)</td>
<td>0.45</td>
</tr>
<tr>
<td>Trauma within 2 mo</td>
<td>1 (9)</td>
<td>14 (14)</td>
<td>1.00</td>
</tr>
<tr>
<td>Creatinine &gt;2.0 mg/dL</td>
<td>1 (9)</td>
<td>15 (16)</td>
<td>1.00</td>
</tr>
<tr>
<td>In-hospital bleeding</td>
<td>4 (36)</td>
<td>15 (16)</td>
<td>0.10</td>
</tr>
<tr>
<td>Recurrent PE at 90 d</td>
<td>...</td>
<td>13 (14)</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Data are numbers of patients with percentages in parentheses. LV indicates left ventricular.

References

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