Short-Term Clinical Outcome of Patients With Acute Pulmonary Embolism, Normal Blood Pressure, and Echocardiographic Right Ventricular Dysfunction

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Background—The role of echocardiographic right ventricular (RV) dysfunction in predicting clinical outcome in clinically stable patients with pulmonary embolism (PE) is undefined. In this study, we assessed the prevalence and clinical outcome of normotensive patients with RV dysfunction among a broad spectrum of PE patients.

Methods and Results—This prospective clinical outcome study included cohort of 209 consecutive patients (age, 65 ± 15 years) with documented PE. Acute RV dysfunction was diagnosed in the presence of at least one of the following: RV dilatation (without hypertrophy), paradox septal systolic motion, and Doppler evidence of pulmonary hypertension. Four groups were identified: 28 patients presenting with shock or cardiac arrest (13%), 19 hypotensive patients without shock (9%), 65 normotensive patients with echocardiographic RV dysfunction (31%), and 97 normotensive patients without RV dysfunction (47%). Among normotensive patients with RV dysfunction, 6 (10%) developed PE-related shock after admission: 3 of these patients died, and 3 were successfully treated with thrombolytic agents. In comparison, none of the 97 normotensive patients without RV dysfunction developed shock or died as a result of PE.

Conclusions—A significant proportion (31%) of normotensive patients with acute PE presents with RV dysfunction; these patients with latent hemodynamic impairment have a 10% rate of PE-related shock and 5% in-hospital mortality and may require aggressive therapeutic strategies. Conversely, normotensive patients without echocardiographic RV dysfunction have a benign short-term prognosis. Thus, early detection of echocardiographic RV dysfunction is of major importance in the risk stratification of normotensive patients with acute PE. (Circulation. 2000;101:2817-2822.)

Key Words: embolism ■ shock ■ echocardiography

A correlation has been reported between echocardiographic right ventricular (RV) dysfunction and clinical outcome in patients with objectively confirmed pulmonary embolism (PE).1-12 Patients with echocardiographic RV dysfunction are known to be at risk of subsequent clinical worsening and PE-related death and may benefit from more aggressive therapeutic strategies, including thrombolytic treatment.13,14 However, the prognostic value of RV dysfunction in patients with PE and normal blood pressure has not been specifically assessed. Because normotensive patients with RV dysfunction represent a large proportion of patients with PE, the benefits of extending thrombolytic treatment to this subgroup need to be weighted against potential disadvantages in terms of bleeding risk and added costs.15 The aim of this study was to evaluate the prevalence and short-term prognosis of patients with objectively confirmed PE, normal blood pressure, and echocardiographic RV dysfunction.

Methods

Patients

Between 1994 and 1997, 388 consecutive patients with clinical suspicion of PE were examined at the Emergency Department of the Azienda Ospedaliera Careggi in Florence, Italy. The initial assessment included clinical history and physical examination, chest radiograph, 12-lead ECG, arterial blood gas analysis, echocardiography, and lower-limb venous ultrasonography. A subsequent evaluation was performed with lung perfusion scan and/or spiral CT scan; pulmonary angiography was performed in those patients lacking a definite PE diagnosis at this stage. Autopsy was performed in patients who died without a definite diagnosis of PE. Thus, PE was excluded in 179 of the 388 patients (46%). The remaining 209 patients (age, 65±15 years; range, 18 to 90 years; 84 men, 125 women) with objectively confirmed PE were included in this prospective clinical outcome study.

Echocardiographic Examination

Standard 2-dimensional echo Doppler examination was performed ≤1 hour from admission with Toshiba SSH140A equipment with 2- and 3.75-MHz probes. Patients with ≥1 of the following were
considered to have acute RV dysfunction: (1) RV dilatation (end-diastolic diameter >30 mm or RV/left ventricular end-diastolic diameter ratio >1 in 4-chamber view), (2) paradox septal systolic motion, and (3) pulmonary hypertension (Doppler pulmonary acceleration time <90 ms or the presence of an RV/atrial gradient >30 mm Hg). However, these signs of RV overload were not considered acute in the presence of RV wall hypertrophy (free wall thickness >7 mm).

Color Venous Duplex Scanning
Examination was performed ≤3 hours from hospital admission with Toshiba SSA 270A equipment with 5- and 7.5-MHz probes. Lack of vein compressibility was interpreted as a positive result and was confirmed with color-flow imaging and pulsed-wave Doppler analysis. Absent or reduced flow, lack of respiratory variation, and failure to increase flow with calf compression were used to confirm the diagnosis. Pelvic and upper limb veins were routinely examined in patients with a negative lower-limb scan.

Perfusion Lung Scan
Lung scans were performed with 99mTc-labeled human albumin microspheres. Six views were required. A normal or near-normal lung scan excluded PE, and a high-probability scan (clear-cut perfusion defects of ≥1 pulmonary segments, mismatched at chest radiograph) confirmed the diagnosis. Patients with intermediate-probability scans underwent CT scan and/or angiography.

High-Resolution CT
A direct scan of the lungs was obtained with a Somatom Plus 4 CT scanner (Siemens) with 1-mm slices every 20 mm and standard sequential acquisition technique. After injection of contrast material, adjacent 3-mm slices were obtained over the hilar region with the spiral acquisition technique. Total scan time ranged from 5 to 10 minutes.

Pulmonary Angiography
Nonionic contrast material was injected into the main pulmonary artery. In patients with uncertain PE diagnosis, selective injections were performed with oblique views. The diagnosis of PE required direct visualization of the embolus or an intraluminal filling defect constant in ≥2 different views or after repeated injections.

Management Strategies
Intravenous heparin was started as soon as PE was suspected with a bolus dose of 80 IU/kg, followed by an 18-IU · kg⁻¹ · h⁻¹ infusion rate, later adjusted to maintain the activated partial thromboplastin time between 60 and 90 seconds in patients with confirmed diagnosis. All patients with clinical signs of hemodynamic impairment or echocardiographic RV dysfunction were observed for 6 months, with the dose adjusted to maintain the international normalized ratio between 2 and 3.

| TABLE 1. General Features of 209 Consecutive Patients With Documented PE |
|-----------------|---|
| Age, y          | 65±15 |
| Female, n (%)   | 84 (60) |
| Risk factors for PE, n (%) |  |
| Previous DVT/PE | 99 (47) |
| Cardiopulmonary disease | 52 (25) |
| Cancer          | 40 (19) |
| Immobilization  | 66 (32) |
| Recent surgery  | 51 (24) |
| Symptoms on presentation, n (%) |  |
| Syncope         | 23 (11) |
| Chest pain      | 83 (40) |
| Dyspnea         | 153 (73) |
| High-probability lung scan, n (%) | 148 (71) |
| Documented DVT, n (%) | 123 (59) |
| Caval filter implantation, n (%) | 10 (5) |
| Thrombolyis, n (%) | 34* (16) |

DVT indicates deep venous thrombosis.
*In 24 patients with massive PE and 10 with temporary caval filters for massive proximal floating.

Definition of Patient Subgroups Based on Clinical Presentation
At initial evaluation, patients were defined as hypotensive and normotensive if they had a systolic pressure <100 mm Hg or ≥100 mm Hg, respectively. Hypotensive patients were defined as being in shock only if presenting with associated signs of systemic hypoperfusion (clouded sensorium, oliguria, cold and clammy skin, and lactic acidosis at arterial blood gas analysis). Thus, on the basis of the combination of clinical and echocardiographic findings, 4 different patient profiles were defined for prognostic assessment: (1) patients presenting with shock (or cardiac arrest), (2) hypertensive patients without shock, (3) normotensive patients with RV dysfunction, and (4) normotensive patients without RV dysfunction.

Statistical Analysis
Data were expressed as mean±SD. We used Student’s t test for comparison of normally distributed data and the χ² test for comparison of noncontinuous variables expressed as proportions. Univariate and multivariate analyses for the assessment of independent risk predictors were performed by use of the Cox regression model.

Results
Diagnosis of PE
In the 209 patients, the diagnosis of PE was obtained on the basis of a high-probability lung scan in 145 (69%), a positive CT scan in 31 (15%), and a positive pulmonary angiography in 29 (14%). In 4 patients who died on admission (2%), PE was diagnosed at autopsy: in 3, PE had been strongly suspected from the clinical and echocardiographic findings, whereas in 1 patient, a ruptured abdominal aortic aneurysm had been suspected.

Clinical and Echocardiographic Profiles on Admission
The clinical presentation of PE ranged from severe shock and respiratory failure to only mild symptoms (Table 1). Of the 209 study patients, 162 (78%) were clinically stable and normotensive, whereas 47 (22%) presented a systolic blood...
pressure <100 mm Hg (the Figure). Of the latter, 28 were judged to be in shock, including the 4 patients who presented with cardiac arrest or died shortly after admission. The remaining 19 patients presented with hypotension but no indications of shock (the Figure).

Echocardiographic examination was performed in all patients except 2 who presented with cardiac arrest. Adequate 2-dimensional images were obtained for all patients, whereas an accurate Doppler evaluation was technically feasible in 161 (77%). A total of 110 patients (53%) were judged to have acute RV dysfunction with ≥1 of the following: RV dilatation (n=89), systolic flattening of the interventricular septum (n=48), and Doppler evidence of pulmonary hypertension (n=62). Six normotensive patients with chronic respiratory disease and evidence of RV dysfunction associated with RV free wall hypertrophy (>7 mm) were considered to have chronic rather than acute RV dysfunction. Interobserver and intraobserver agreement for the definition of RV dysfunction was 94% and 96%, respectively.

From the clinical and echocardiographic findings on admission, the patients were categorized as follows (the Figure): (1) patients presenting with shock or cardiac arrest (n=28, 13%), (2) hypotensive patients without shock (n=19, 9%), (3) normotensive patients with RV dysfunction (n=65, 31%), and (4) normotensive patients without RV dysfunction (n=97, 47%).

The clinical features of normotensive patients with and without RV dysfunction are compared in Table 2. On average, patients with RV dysfunction had a lower systolic blood pressure and were more tachycardic, hypoxic, and hypocarbic on presentation. There was no difference in the prevalence of smoking history or chronic lung disease between the 2 groups (Table 2).

**Treatment**

Intravenous heparin was immediately started in all patients at the time PE was suspected. In 2 of the 4 patients who died suddenly (<1 hour after admission), heparin treatment was not implemented because of lack of time (n=1) or a wrong initial diagnosis (n=1). Thrombolytic treatment was initially administered to 31 patients (15%), including 16 patients presenting with shock, 5 patients with minor hemodynamic impairment, and 10 normotensive patients with floating venous thrombosis after percutaneous vena cava filter insertion. Three additional normotensive patients with RV dysfunction and subsequent clinical deterioration received rtPA (n=2) or urokinase (n=1) 4 to 7 hours after the diagnosis of PE (the Figure and Table 3). Of the 34 patients treated with thrombolytic agents, 2 (6%) had severe treatment-related complications, including 1 nonfatal cerebral hemorrhage and 1 hematuria requiring urgent transfusion; 8 additional patients (24%) suffered minor extracerebral bleeding not requiring transfusion.

In the 12 patients presenting with shock who did not receive thrombolytic treatment, the following reasons were given: advanced age (>85 years; n=4), advanced cancer (n=3), sudden death (n=2), recent surgery (n=1), recent stroke (n=1), and misdiagnosis (n=1).

**In-Hospital Mortality and PE-Related Clinical Outcome**

Of the 209 study patients, 17 (8%) died during admission. Of these 17 deaths, 13 were judged to be directly related to PE;
the remaining 4 were due to cancer (n=3) and heart failure (n=1; the Figure). The 13 PE-related deaths were distributed as follows (the Figure): 9 among the 28 patients with shock (32%), 1 among the 19 patients with minor hemodynamic impairment (5%), 3 among the 65 normotensive patients with RV dysfunction (5%), and 0 among the 97 normotensive patients without RV dysfunction (the Figure). Echocardiography thus showed a 100% negative predictive value for PE-related death, although its positive predictive value was very low (Table 4). Of the 13 PE-related deaths, only 2 occurred in patients receiving urgent thrombolysis in the group presenting with shock; the remaining 11 were among those patients in whom thrombolysis had not been instituted by the physician in charge.

Among the 65 patients with RV dysfunction who were normotensive on presentation, a total of 6 patients (10%) experienced clinical deterioration and developed shock during the acute phase judged to be caused by PE despite adequate anticoagulation with heparin (Table 3). Of these 6 patients, 3 died shortly after the event, as mentioned above, whereas 3 were successfully treated with urgent thrombolysis instituted at the time of clinical deterioration (Table 3). Of note, 2 of the 3 patients who died had absolute contraindications to thrombolytic treatment, and 1 was an elderly patient with metastatic cancer. At multivariate analysis, the following variables were associated with short-term clinical worsening and/or PE-related death among the 65 normotensive patients with RV dysfunction: advanced age, recent trauma or orthopedic treatment, and lower systolic blood pressure and dizziness at presentation (Table 5).

### TABLE 3. Clinical Features of 6 Normotensive Patients With RV Dysfunction on Admission and Subsequent Clinical Worsening or Death

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Sex</th>
<th>Associated Conditions</th>
<th>Mode of Diagnosis</th>
<th>Initial Treatment</th>
<th>Time to Shock,* h</th>
<th>Contraindications to Thrombolytic Treatment</th>
<th>Thrombolytic Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>53</td>
<td>F</td>
<td>Traumatic leg fracture</td>
<td>Lung scan, spiral CT</td>
<td>Heparin</td>
<td>4</td>
<td>Relative</td>
<td>rtPA</td>
<td>Discharged</td>
</tr>
<tr>
<td>81</td>
<td>M</td>
<td>Trauma, orthopedic surgery</td>
<td>Lung scan</td>
<td>Heparin</td>
<td>5</td>
<td>Relative</td>
<td>rtPA</td>
<td>Discharged</td>
</tr>
<tr>
<td>85</td>
<td>F</td>
<td>Poor mobilization</td>
<td>Angiography</td>
<td>Heparin</td>
<td>7</td>
<td>None</td>
<td>UK</td>
<td>Discharged</td>
</tr>
<tr>
<td>62</td>
<td>M</td>
<td>Trauma, surgery, previous DVT</td>
<td>Lung scan</td>
<td>Heparin</td>
<td>11</td>
<td>Absolute</td>
<td>No†</td>
<td>Died</td>
</tr>
<tr>
<td>86</td>
<td>M</td>
<td>Cancer</td>
<td>Lung scan</td>
<td>Heparin</td>
<td>24</td>
<td>Relative</td>
<td>No‡</td>
<td>Died</td>
</tr>
<tr>
<td>87</td>
<td>F</td>
<td>Cancer, trauma</td>
<td>Lung scan</td>
<td>Heparin</td>
<td>20</td>
<td>Absolute</td>
<td>No‡</td>
<td>Died</td>
</tr>
</tbody>
</table>

UK indicates urokinase; DVT, deep venous thrombosis.
*From diagnosis of PE
†Absolute contraindication to thrombolytic treatment.
‡Relative contraindication to thrombolytic treatment.

### Discussion

#### Role of Echocardiography in Risk Stratification of Patients With PE

Echocardiography has progressively achieved a prominent role in the diagnosis and clinical assessment of patients with PE. In patients with normal blood pressure and no signs of shock on presentation, RV dysfunction provides indirect evidence of severe pulmonary artery obstruction and impending hemodynamic failure (Table 2). Among normotensive patients, only the subgroup with evidence of RV dysfunction experienced adverse PE-related outcome (the Figure). Hence, the negative predictive value of echocardiography for PE-related death proved to be 100% in this particular patient population, although its positive predictive value was low (Table 4). From these results, echocardiographic examination of normotensive patients with PE is mandatory for early detection of latent hemodynamic impairment, provides valuable information for risk stratification, and appears to be most relevant as a screening test for the identification of low-risk patients.

### Prevalence and Prognosis of Latent Hemodynamic Impairment

In the heterogeneous spectrum of PE, normotensive patients with RV dysfunction represent the wide gray area between mild disease and severe hemodynamic impairment. In our study, normotensive patients presenting with RV dysfunction represented 31% of the total cohort and 40% of all normotensive patients with PE. These findings are in agreement with the existing literature, indicating that patients with latent hemodynamic impairment represent a substantial subgroup among unselected patients with PE.

During the hospital admission, 10% of the 65 patients with latent hemodynamic impairment (n=6) developed shock as a result of PE recurrence, half of whom died soon after admission (the Figure). In the remaining 3 patients, life-
saving delayed thrombolysis was successfully instituted. Of note, the 3 patients who died were not considered candidates for thrombolysis because of specific contraindications and general clinical conditions (Table 3). At multivariate analysis, the clinical variables associated with the development of shock after admission were represented by advanced age, recent trauma or orthopedic treatment, and dizziness and lower systolic blood pressure at presentation. PE-related mortality among the 65 patients with latent hemodynamic impairment (5%) was significantly lower than that of patients presenting with shock (32%; \(P<0.0005\); the Figure); however, it was not negligible, especially compared with the absent PE-related mortality among normotensive patients without RV dysfunction. In particular, the 5% mortality rate was identical to that of patients with minor clinical manifestations of hemodynamic impairment (the Figure) and similar to those observed in patients with major PE and no evidence of cardiogenic shock by other researchers.\(^{21,22}\) Therefore, once patients with shock are excluded, the detection of RV dysfunction defines a large subgroup of patients at intermediate short-term risk of PE-related mortality that seems to be independent of the clinical manifestations of hemodynamic impairment.

Other studies have addressed the relevance of RV dysfunction as a predictor of adverse outcome in patients with PE. However, to the best of our knowledge, ours is the first prospective study to analyze the issue specifically in patients who are clinically stable on presentation. This is of primary importance because aggressive therapeutic strategies (including widespread use of thrombolysis) have been advocated for patients with RV dysfunction, although their potential benefit in the absence of overt cardiogenic shock is still unresolved. At present, the available data on the prognosis of patients with pulmonary embolism and RV dysfunction emanate from multicenter registries with potential patient selection bias,\(^{23,24}\) originate from studies designed for other purposes,\(^{21,22}\) or have been described regardless of their clinical presentation, as in Reference 25. In this last study, among patients with RV dysfunction, no distinction is made between patients presenting in shock who are known to have a severe prognosis and definitely require thrombolysis and those who are clinically stable on presentation and may benefit from conservative treatment. As a consequence, the reported mortality figure of 14% in patients with PE and RV dysfunction is misleading in that it presumably represents an average value between the high mortality rate of patients presenting with shock (32% mortality in our study) and the lower mortality rate of stable patients with RV dysfunction (5% in our study).

### Table 5. Variables Associated With Short-Term Clinical Worsening and/or PE-Related Death in 65 Normotensive Patients With Documented PE and RV Dysfunction

<table>
<thead>
<tr>
<th>Age &gt;80 y, n (%)</th>
<th>Stable Course (n=59)</th>
<th>Worsening/Death (n=6)</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent trauma/orthopedic, n (%)</td>
<td>9 (15)</td>
<td>4 (67)</td>
<td>&lt;0.01</td>
<td>0.08</td>
</tr>
<tr>
<td>Preexisting cardiopulmonary disease, n (%)</td>
<td>19 (32)</td>
<td>2 (33)</td>
<td>NS</td>
<td>...</td>
</tr>
<tr>
<td>Risk factors for PE, n (%)</td>
<td>20 (34)</td>
<td>1 (17)</td>
<td>NS</td>
<td>...</td>
</tr>
<tr>
<td>Dizziness, n (%)</td>
<td>5 (8)</td>
<td>2 (33)</td>
<td>0.07</td>
<td>0.1</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>130±17</td>
<td>105±29</td>
<td>0.005</td>
<td>0.05</td>
</tr>
<tr>
<td>ECG heart rate, bpm</td>
<td>105±21</td>
<td>107±26</td>
<td>NS</td>
<td>...</td>
</tr>
<tr>
<td>Pao2, mm Hg</td>
<td>63±14</td>
<td>54±10</td>
<td>NS</td>
<td>...</td>
</tr>
<tr>
<td>RV dimensions, mm</td>
<td>32±6</td>
<td>33±6</td>
<td>NS</td>
<td>...</td>
</tr>
</tbody>
</table>

BP indicates blood pressure.

**Relevance of Latent Hemodynamic Impairment on Management Strategies**

The finding that all normotensive patients without evidence of RV dysfunction had a favorable prognosis on standard heparin treatment is relevant because of its potential implications in disease management.\(^{25}\) Although caution is still required at this stage,\(^{24}\) our data support the possibility of less aggressive treatment for patients with PE but no clinical or echocardiographic signs of instability. Particularly appealing is the possibility of considering home treatment with low-molecular-weight heparin in these patients, following the existing guidelines for the treatment of deep venous thrombosis, with considerable economic and lifestyle benefits.\(^{26}\)

The optimal acute management strategy for clinically stable patients with evidence of RV dysfunction is as yet unclear, and although it has been suggested that thrombolysis may improve the outcome in this particular subgroup,\(^{14,23}\) such hypotheses are still under debate.\(^{15}\) Results of the present study suggest that the detection of RV dysfunction represents an important prognostic determinant and is associated with a significant prevalence of severe adverse PE-related outcome. However, its positive predictive value may be too low to warrant aggressive treatment in all normotensive patients with RV dysfunction. According to our study, the decision of extending thrombolytic treatment to all patients with RV dysfunction would lead to a 5-fold increase in the use of such treatment among patients with PE and presumably to a comparable rise in treatment-related complications. Therefore, such decision needs to be supported by prospective randomized trials, which are still not available.

At present, all patients with PE and latent hemodynamic impairment should be carefully monitored during the initial phase of the hospital admission, and patients with low
bleeding risk should probably be considered for immediate thrombolysis. This decision, however, becomes more challenging for the substantial subgroup of patients with ≥1 contraindications (including advanced age). In these patients at high bleeding risk, it may be wiser to postpone the decision of initiating thrombolysis and to select candidate patients for “delayed” thrombolysis on the basis of the short-term clinical course, as can be inferred by the MAPPET study (Management strategy And Prognosis of Pulmonary Embolism Trial) and the present study (Table 3).

Study Limitations
Our results are confined to the in-hospital period. Therefore, no conclusion can be drawn as to the long-term consequences of latent hemodynamic impairment in patients with PE. However, a recent study by Ribeiro et al reported a 3-fold increase in mortality at 1 year in patients with RV dysfunction at presentation compared with those without, suggesting that the prognostic implications of RV dysfunction in patients with acute PE may be extended long term.

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References
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