Pulmonary Embolism
One-Year Follow-Up With Echocardiography Doppler and Five-Year Survival Analysis

Ary Ribeiro, MD; Per Lindmarker, MD; Hans Johnsson, MD, PhD; Anders Juhlin-Dannfelt, MD, PhD; Lennart Jorfeldt, MD, PhD

Background—The long-term prognosis for patients with pulmonary embolism (PE) is dependent on the underlying disease, degree of pulmonary hypertension (PH), and degree of right ventricular (RV) dysfunction. A precise description of the time course of pulmonary artery pressure (PAsP)/RV function is therefore of importance for the early identification of persistent PH/RV dysfunction in patients treated for acute PE. Other objectives were to identify variables associated with persistent PH/RV dysfunction and to analyze the 5-year survival rate for patients alive 1 month after inclusion.

Methods and Results—Echocardiography Doppler was performed in 78 patients with acute PE at the time of diagnosis and repeatedly during the next year. A 5-year survival analysis was made. The PAsP decreased exponentially until the beginning of a stable phase, which was ≤38 days. The recovery of RV function occurred during the same time period. Risk factors for persistent PH/RV dysfunction and the 5-year mortality rate were analyzed using multiple logistic regression models. A PAsP of >50 mm Hg at the time of diagnosis of acute PE was associated with persistent PH after 1 year. The 5-year mortality rate was associated with underlying disease. Only patients with persistent PH in the stable phase required pulmonary thromboendarterectomy within 5 years.

Conclusions—An echocardiography Doppler investigation performed 6 weeks after diagnosis of acute PE can identify patients with persistent PH/RV dysfunction and may be of value in planning the follow-up and care of these patients.

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Key Words: pulmonary heart disease n echocardiography n follow-up studies n statistics

Pulmonary hypertension (PH) and right ventricular (RV) overload are frequent at the time of diagnosis of pulmonary embolism (PE).1–5 The regress of increased pulmonary artery systolic pressure (PAsP) to near-normal values can be expected to occur in the majority of the patients within 3 weeks.6 The occurrence of chronic thromboembolic pulmonary hypertension (CTPH) after a diagnosis of acute PE is considered to be rare.2,7,8 It has been suggested, however, that this condition is more common than generally believed.9

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The long-term prognosis of patients with CTPH and without previous cardiopulmonary disease is related to the level of PA pressure and the presence of RV failure.10 However, the course within the year after the diagnosis of acute PE has not been well characterized. The identification of persistent PH/RV dysfunction in patients treated for acute PE may be erroneous or delayed if the course of PAsP/RV function is not well described.

This study was designed to (1) describe the course of PAsP and RV function within the year after the diagnosis of acute PE, (2) test the hypothesis that there are clinical and echocardiographic variables at the time of diagnosis of acute PE associated with an increased risk for the presence of PH or RV dysfunction 1 year later, and (3) determine which variables associated with PE were relevant for the 5-year survival of patients alive 1 month after the diagnosis of PE.

Methods

Study Design and Patient Selection
This was a prospective, descriptive, single-center follow-up study without randomization for treatment. The inclusion period was from August 1988 through September 1992. A more detailed description of the process of patient selection has been given previously.5 The inclusion criteria were (1) patients with clinical suspicion of acute PE referred for diagnostic investigation at our hospital; (2) age of ≥18 years; (3) diagnosis of PE based on ventilation/perfusion scan, pulmonary angiography, or both and a same-day investigation with echocardiography Doppler (echo-Doppler); and (4) feasibility for repeated echo-Doppler investigations at our institution during the
year after inclusion. The day on which the diagnosis of PE was made was defined as day 1. Repeated echo-Doppler investigations were planned for days 4, 8, 30, 90, 180, and 365.

During the study period, 128 patients fulfilled the diagnostic criteria. Fifty patients were not included in the follow-up because follow-up was considered unethical or not feasible (25 patients), resources for echo-Doppler investigation were not available on the day of diagnosis (13), patients were not reported to the investigators (8), patients were not willing to participate in repeated examinations (2), or the diagnosis of PE was made at the preliminary evaluation of the lung scintigraphy. Thus, 78 patients were initially included.

The study was approved by the Ethics Committee of the Karolinska Hospital.

Baseline Variables
The baseline variables analyzed were age, gender, duration of symptoms, and underlying disease, as previously defined. Malignancy was defined as known disease at the time of inclusion.

Recurrent PE
For the period of 1 month to 1 year after inclusion, patients with symptoms suggesting PE and with new perfusion defects on the lung scan were interpreted as having recurrent PE.

Echo-Doppler
A transthoracic echo-Doppler was performed immediately after the diagnosis of PE and repeatedly during the year of follow-up. Assessment of RV wall motion and calculation of the PAsP, as well as the reproducibility for these measurements, have been described previously.

Pulmonary Artery Systolic Pressure
The tricuspid regurgitation (TR) Doppler signal at day 1 was not detectable in 8 patients, and they were excluded.

For the remaining 70 patients, the values of PAsP obtained from repeated examinations were plotted against time (Figure 1). A course pattern was found that apparently had 2 phases: an initial dynamic phase and a late stable phase. The stable phase appeared start 1 month after diagnosis of acute PE. We assumed that the time course of the variable PAsP could be characterized by an initial exponential phase \( b_2 \exp(b_3 \times \text{time}) \) added to linear phase \( (b_0 + b_1 \times \text{time}) \) and was applied only in patients in whom value at day 1 exceeded \( b_2 \) by \( >1.96 \times 1.96 \times \text{day-to-day intrapatient variation of measurements (SD}_{\text{meas}} \) (B). C. Calculation of time \( t_s \) at which PAsP had declined to “stable” linear phase.

The time at which the PAsP value for each separate patient had declined to the stable phase level \( t_s \) was considered to be when the PAsP value estimated the equation \( y=b_0+b_1+1.96 \times \text{sd}_{\text{meas}} \) (Figure 2A). To obtain a reasonable basis for a least-squares adaptation to the equation, we excluded from further analyses 26 patients with \( <5 \) measurements during the follow-up period, leaving 44 patients for subsequent analyses. Furthermore, we considered the 4-parameter model relevant only if the day-1 value exceeded an average value, as estimated through extrapolation from the linear (stable) phase, by \( >1.96 \times 1.96 \times \text{day-to-day intrapatient variation of measurements (SD}_{\text{meas}} \) (Figure 2B). To estimate SD_{\text{meas}} values, we applied for each separate patient a least-squares fit of observations on day 31 through day 365 to the equation \( y=b_0+b_1+1.96 \times \text{sd}_{\text{meas}} \). The sum of squares obtained was added \( (SS_{\text{sum}}) \), and a total root-mean-square value (RMS_{\text{sum}}) was calculated according to RMS_{\text{sum}}=\frac{\sqrt{[1/(N-n-2n)]}}{\Sigma SS_{\text{obs}}}, \text{ where N is the total number of observations, and n is the number of patients. SD}_{\text{meas}} (RMS_{\text{sum}}) was found to be 3.07. Seven patients were excluded, leaving 37 patients for subsequent analyses. For each of these patients, we performed a least-squares adaptation to the 4-parameter equation by applying a nonlinear regression model.
RV Function
Hypokinesia of RV was classified as RV-A (hypokinesia 0 and 1+) or RV-B (2+ or 3+), as described previously.1 Each observation was assigned to 1 of the "nominal" predetermined occasions. To describe the time course of RV function, 3 criteria were required: a echocardiographic baseline observation (day 1), ≥1 additional observation during the period assumed to be dynamic, and a completed 1-year follow-up; 3, 5 and 14 patients, respectively, were thereby excluded, leaving 56 patients for the 1-year serial analyses of RV function.

Echo-Doppler Status at 1-Year Follow-Up
Patients were classified into 2 groups: those in group 1 had an PAsP of ≤30 mm Hg or no detectable TR Doppler signal and RV-A, and those in group 2 had an PAsP of >30 mm Hg or RV-B.

Five-Year Survival Analysis
A 5-year survival analysis was made in September 1997. Patients who were analyzed were those who survived longer than 1 month after the day on which the diagnosis of PE was made. Data were collected from the Swedish Death Register; if PE was assigned as the immediate or underlying cause of death in the death certificate, patients were classified as having died from PE.

Statistical Analysis
Data with normal distribution are presented as mean±SD or as median and range. All probability values are 2-tailed, and values of <0.05 were considered statistically significant. The Student’s t, Wilcoxon rank sum, χ2, and Fisher’s exact test were used when applicable.

To identify at the time of diagnosis predictors of adverse outcome defined as persistent PH or RV systolic dysfunction at 1-year follow-up, a multiple logistic regression analysis was performed. Patients who interrupted the follow-up or died during the period were classified as belonging to group 2, according to the principle of "pragmatic approach."11 The variables entered in the model were classified as belonging to group 2, according to the principle of

TABLE 1. Characteristics at Inclusion of 78 Patients Categorized According to Status at 1-Year Follow-Up

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1 (n=44)</th>
<th>Group 2 (n=34)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61 (21–80)</td>
<td>71 (29–85)</td>
<td>0.001</td>
</tr>
<tr>
<td>Male, n</td>
<td>30</td>
<td>18</td>
<td>0.24</td>
</tr>
<tr>
<td>Duration of symptoms ≤14 days, n</td>
<td>31</td>
<td>20</td>
<td>0.34</td>
</tr>
<tr>
<td>Malignancy, n</td>
<td>3</td>
<td>4</td>
<td>0.69</td>
</tr>
<tr>
<td>Congestive heart failure, n</td>
<td>4</td>
<td>7</td>
<td>0.19</td>
</tr>
<tr>
<td>Previous myocardial infarction, n</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Previous venous thromboembolic episode, n</td>
<td>11</td>
<td>7</td>
<td>0.79</td>
</tr>
<tr>
<td>Chronic lung disease, n</td>
<td>5</td>
<td>2</td>
<td>0.46</td>
</tr>
<tr>
<td>Thrombolytic therapy, n</td>
<td>18</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>RV systolic dysfunction, n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 or 1+</td>
<td>18</td>
<td>9</td>
<td>0.24</td>
</tr>
<tr>
<td>2+ or 3+</td>
<td>25</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>PAsP, mm Hg</td>
<td>43±11</td>
<td>56±14</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV systolic dysfunction, n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 or 1+</td>
<td>39</td>
<td>28</td>
<td>0.71</td>
</tr>
<tr>
<td>2+ or 3+</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

Group 1 indicates PAsP≤30 mm Hg or no detectable tricuspid regurgitation and RV dysfunction grade 0 or 1+ at 1-year follow-up; group 2, PAsP>30 mm Hg or RV dysfunction 2+ or 3+.

(44±13 mm Hg, P=0.0009). No other differences were found in relation to treatment groups. Recurrent PE was diagnosed in 6 patients (6 of 78, 7.7%) but did not influence the final course of PAsP during the follow-up year.

Course of PAsP/RV Function Within 1 Year
The curves describing the course for the mean (37 patients), in relation to groups 1 and 2, generated with the 4 parameters b0, b1, b2, and b3 of the function PAsP=b0+b1×time+b2×exp(b3×time) are presented in Figure 3.

As expected (by definition), the parameter b0 was higher in group 2. No significant differences were found between the 2 groups for the degree (b2) or rate (b3) of reduction in PAsP. The time (in days) at which the PAsP had reached the stable phase level (c) was essentially the same for both groups (group 1, 7.3 [0.3 to 37.3]; group 2: 6.7 [0.1 to 20.0]).

Figure 3. Course of PAsP in relation to status at 1-year follow-up. Group 1 indicates patients with PAsP of ≤30 mm Hg or no detectable tricuspid regurgitation and RV dysfunction of grade 0 or 1+. Group 2 indicates patients with PAsP of >30 mm Hg or RV dysfunction of 2+ or 3+. Number within parentheses represents SD or range. *P<0.01.
The parameter $b_1$, which describes the slope of the apparently stable phase, was not significantly different from zero ($0.00231 \pm 0.0876$). The time to achieve the stable phase was $\leq 21$ days for 90% of patients and $\leq 38$ days for all patients (Figure 4).

The treatment received in the acute phase produced no significant difference in the time to achieve the stable phase (thrombolysis, 4.9 days [0.1 to 21 days]; heparin, 4.6 [0.4 to 37 days]; $P = 0.9$) or in the level of PAsP estimated for the stable phase (29 [21 to 60] versus 27 [17 to 37], $P = 0.19$).

The nonlinear estimation could not be applied in 33 patients: 1 had a course that did not fit the model, 6 lacked significant variability, and 26 patients had $\leq 5$ measurements during the follow-up period (3 follow-up visits but no detectable TR Doppler signal $\leq 5$ times, 5 more visits, death, or refusal to fulfill the follow-up program). The pattern of changes in PAsP for this subgroup of 33 patients was essentially the same pattern as that seen for the entire group.

Of the 56 patients who fulfilled the criteria for analysis of repeated measurements for degree of RV hypokinesis, 36 (64%) had significant RV dysfunction at the time of diagnosis of PE (day 1). At the 1-year follow-up, only 3 of these patients had persistent RV dysfunction, whereas the remaining 33 patients had normal RV systolic function. In the great majority of patients, RV systolic function had normalized by day 8 (7 days [5 to 13 days]), as shown in Table 2. One patient recovered RV function between days 8 and 30.

### Status at 1-Year Follow-Up

Table 1 shows selected characteristics for the 78 patients at inclusion according to classification into group 1 or 2 at the end of the 1-year follow-up period. Patients with persistent PH/RV dysfunction (group 2) were significantly older and presented with a higher level of PAsP at day 1.

As shown in Table 3, in a multiple logistic regression model, age of $> 70$ years and PAsP of $> 50$ mm Hg at the time of the diagnosis of PE were independent variables significantly associated with an increased risk of persistent PH/RV dysfunction.

### Five-Year Survival Analysis

Of the 73 patients alive 1 month after the diagnosis of acute PE, 12 (16.4%) died during the subsequent 5 years. The causes of death were cancer (5), heart failure (4), pneumonia (1), cardiac arrhythmia (1), and cerebrovascular insult (1). None of the deaths were attributed to PE.

Table 4 shows selected characteristics for the 73 patients at 1-month follow-up in relation to 5-year survival rates. In a multiple logistic regression model, variables significantly associated with the 5-year mortality rate were diagnosis of cancer (OR, 22.6; 95% CI, 3.5 to 215.6), age (OR, 20.9; 95% CI, 1.3 to 367.0), and PAsP $> 35$ mm Hg (OR, 9.2; 95% CI, 1.5 to 77.5).

Three patients in group 2 underwent pulmonary thromboendarterectomy at 12, 24, and 44 months after inclusion in the study. All the 3 patients were alive at the end of the 5-year observation period.

### Discussion

The results of the study show that in patients with acute PE and increased pulmonary artery pressure, the pattern of the change in PAsP with time is characterized by an initial dynamic phase followed by a stable phase, which is achieved within 30 days in $> 90\%$ of patients. The recovery of RV wall motion occurs in almost all patients within the same period of time. Consequently, the identification of persistent PH, RV dysfunction, or both can be made soon after the diagnosis of acute PE.
Dalen et al.\textsuperscript{6} reported the results of repeated catheterization after acute PE in 15 patients without previous cardiac disease. It was observed that right heart pressures had returned to near-normal values in the majority of patients within 10 to 21 days. In our study, we analyzed the course in 37 patients, all with $\geq 5$ PAsP measurements during 1-year follow-up providing a more detailed description of the course over a longer period. Despite differences in methods and materials between our study and that of Dalen et al, the results are concordant concerning patients who returned to normal PA pressures. In addition, our study demonstrates that patients who do not have a normal PA pressure achieve a stabilization within 1 month.

The relation between clinical and echocardiographic variables at the time of diagnosis and the risk of persistent PH/RV dysfunction has not been analyzed before. In the present study, this risk was calculated to be $\approx 3$ times higher for patients with PAsP of $>50$ mm Hg at the time of diagnosis. Age of $>70$ years was also associated with an increased risk of persistent PH/RV dysfunction. However, because the confidence intervals in the analyses are wide, caution should be used in interpreting the absolute value for increased risk.

The number of patients classified as having persistent PH/RV dysfunction in our study was high compared with previous studies.\textsuperscript{7,8} There several explanations for this. Patients (14 of 78, 17.9%) not evaluated at 1-year follow-up due to withdrawals or death were classified according to the principle of “pragmatic approach”\textsuperscript{11} as having persistent PH/RV dysfunction. Furthermore, the cutoff level for PH at 1-year follow-up was low: PAsP $>30$ mm Hg. However, even with a higher cutoff level ($>40$ mm Hg) for PAsP after 1 year, the number of patients with persistent PH is still considerable (4 of 78, 5.1%). A PAsP of $>70$ mm Hg at the day of diagnosis of PE has been used for differentiating between patients with “acute” and “subacute” or “chronic” PE.\textsuperscript{12,13} In our study, there were 7 patients (7 of 78, 8.9%) with PAsP of $>70$ mm Hg on the day for diagnosis, which represents a considerable number of cases. These findings indicate that there are more patients with significant persis-
hospital mortality rate was 12% in the group not included in follow-up and 6.4% in the group included in the follow-up ($P=0.34$). The 5-year mortality rates were 42% and 21.8%, respectively ($P=0.02$). Based on these analyses, we conclude that the sample included in the 1-year follow-up (n=78) differed from the sample not included (n=50). We cannot discount that results differing from those reported in the present study can be found in a sample including a broader spectrum of patients with PE.

The proportion of patients (41%, 32 of 78) who received thrombolytic therapy was higher than expected. However, if we analyze the 128 patients who were considered for inclusion, this percentage falls to 25%. This figure is in accordance with that reported (23.5%) in a study of patients with PE who were hemodynamically stable at inclusion. 4

A difficult problem in clinical research is how to approach the problem of repeated measurements when the prerequisite for analysis of variance is not filled. 17 In the present study, we analyze the problem of repeated measurements when the prerequisite for analysis of variance is not filled. 17 In the present study, we analyze the problem of repeated measurements when the prerequisite for analysis of variance is not filled. 17

Incompleteness of the data set in the serial analyses of RV function (from 78 to 56) was also a problem. However, if we analyze all patients with $>1$ observation (n=72) or those with $>1$ observation during the stable phase (n=67), the results are essentially the same as those given in Table 2.

We conclude that the pattern for the change with time of PAsP/RV function during the year after an acute episode of PE has an initial dynamic phase of 6 weeks followed by a stable phase. In patients with a PAsP of $>50$ mm Hg at the time of diagnosis of the acute episode, the risk for persistent PH/RV dysfunction increases 3-fold. Five-year follow-up showed that these patients may have further hemodynamic deterioration. Patients at risk may be identified through a systematic echo-Doppler investigation 6 weeks after the day of the diagnosis of acute PE. These findings may have implications in planning the follow-up and care of PE patients.

**Acknowledgments**

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**References**

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