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. 

Key Words: pulmonary heart disease ■ echocardiography ■ follow-up studies ■ 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

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 not made at the preliminary evaluation of the lung scintigraphy (2). 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 PA systolic pressure (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 \( [b_2 \times \exp(b_3 \times t)] \) added to a linear late phase \( (b_0 + b_1 \times t) \) and described by the equation \( y = b_0 + b_1 \times t + b_2 \times \exp(b_3 \times t) \) (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 the day-to-day intrapatient variation of measurements (SDmeas) (Figure 2B). To estimate SDmeas values, we applied for each separate patient a least-squares fit of observations on day 31 through day 365 to the equation \( y = a_0 + a_1 \times t \). The sum of squares obtained were added (SStot), and a total root-mean-square value (RMSmeas) was calculated according to \( RMS_{meas} = \sqrt{[1/(N-2n)] \times SS_{meas}} \), where N is the total number of observations, and n is the number of patients. SDmeas (= RMSmeas) 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.

The time at which the PASp value for each separate patient had declined to the stable phase level \( (t_0) \) was considered to be the day 1. PASp value estimated the equation \( y = b_0 + b_1 \times t + b_2 \times \exp(b_3 \times t) \) was equal to \( y = b_0 + b_1 \times t + 1.96 \times 3.07 \times 6.0 \) (3.07 = SDmeas as determined above). Hence, \( b_1 \times \exp(b_3 \times t) = 6.0 \) and \( t_0 = \ln(6.0/b_2)/b_1 \) (Figure 2C).
RV Function
Hypokinesis of RV was classified as RV-A (hypokinesis 0 and 1+) or RV-B (2+ or 3+), as described previously. 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 a PAsP of ≤30 mm Hg or no detectable TR Doppler signal and RV-A, and those in group 2 had a 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.” The variables entered in the model were those with probability values of ≤0.2 in the univariate analyses between groups 1 and 2 as shown in Table 1. The cutoff level for grouping the continuous variables of age and PAsP in Table 1 was based on receiver operating characteristic curves (ROCs) by identification of the best level for discrimination between groups 1 and 2 at 1 year.

To identify variables associated with a 5-year mortality rate for patients alive 1 month after the diagnosis of PE, a multiple logistic regression analysis was performed as described but using the data given for the 73 patients at 1-month follow-up in relation to 5-year survival rates (see Table 4).

The results of the regression models are presented as odds ratio (OR) with a 95% CI values.

All statistical analyses were made with the use of JMP, version 3.1 (SAS Institute Inc) with the exception of the nonlinear estimation of PAsP, for which (quasi-newtonian method) STATISTICA for Windows 1995 (StatSoft Inc) was used.

Results
At the time of the diagnosis of PE, patient characteristics were similar for the 78 patients initially included in the follow-up and for the 50 patients who were not included, except for patients with known malignancy (7 of 78 versus 16 of 50, P=0.002). The 1-year follow-up program could not be completed in 14 patients (ethical reasons due to the presence of cancer in an advanced stage diagnosed after inclusion or death for 9 patients and refusal to undergo the planned investigations for 5 patients). Thirty-two patients (41%) treated with thrombolytic agents had significantly more RV systolic dysfunction (P<0.0001) and higher PAsP values (55±13 mm Hg) than did those treated with heparin.

### 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>0 or 1+</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>2+ or 3+</td>
<td>25</td>
<td>23</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>0 or 1+</td>
<td>39</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>2+ or 3+</td>
<td>4</td>
<td>4</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+b2exp(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]).
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 $<21$ 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 5 measurements during the follow-up period ($< 5$ follow-up visits but no detectable TR Doppler signal $< 5$ times, $< 5$ follow-up 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 al⁶ 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 ≥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 the approach used to describe dynamic changes in patients with PE who have 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.⁷,⁸ There are 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”⁷¹ (ie, patients with missing echo-Doppler data were classified as group 2). This may have influenced the results shown in Table 3. However, 2 alternative models (1 that included patients missing 1-year echo-Doppler data in group 1 and the other included only the 64 who were actually evaluated at the 1-year follow-up) provided the same results as are given in Table 3. In the alternative model that included the 64 patients, age was not significantly associated with persistent PH/RV dysfunction 1 year later. The alternative analyses⁷⁴ make us confident that the level of PAsP of >50 mm Hg at the day of the diagnosis of PE is a risk factor for persistent PH/RV dysfunction 1 year later.

A weakness of the study was the relative incompleteness of the data set: a reduction from 128 to 78 patients (included in the 1-year echo-Doppler follow-up), from 70 to 37 patients (for serial analyses of PAsP), and from 78 to 56 (for serial analyses of RV function). However, the incompleteness was not due to selection bias but rather to study design and to the methodological approach used to describe dynamic changes of the selected variables.

The overall in-hospital mortality rate (8.6%) in the sample of 128 individuals considered for inclusion in follow-up is similar to that reported by Carson et al (9.5%)¹⁵ and to the mortality rate (8.1%) of hemodynamically stable patients reported by Kasper et al.¹⁶ Based on these observations, we conclude that the sample evaluated for inclusion in follow-up was representative of the population of PE patients who were “hemodynamically stable” at diagnosis.

The sample population for the 1-year echo-Doppler follow-up study included fewer cases of cancer and the patients received thrombolytic therapy more often. The in-
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.

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. In the present study, we approached the problem by studying the continuous variables as a function of time ($y=f(t)$). Based on raw plot for all patients, we set up a model of an initial exponential phase approaching a subsequent linear phase. The data for the individual patient were then adapted to the model by a least-squares fit. With this methodology, variables could be analyzed independently of the precise time of observation, size of the group of patients, and magnitude of variance observed on the corresponding occasion. This approach is less sensitive for missing data than, for instance, ANOVA. Some patients had to be excluded from the final analysis because they did not fulfill the criteria; for example, 1 patient presented a course with an initially increasing PAsP. This patient had progressive RV failure within the follow-up period and underwent successful pulmonary thromboendarterectomy. The proposed model is applicable for the majority of, but not for all patients with a diagnosis of acute PE.

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 $\geq 1$ 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

This work was supported by grants from the Swedish Heart and Lung Foundation, the Karolinska Institute, and the Swedish Medical Research Council (projects 04139 and 07917). We acknowledge Elisabeth Berg, PhD, for advice on statistical analyses.

### References

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

Ary Ribeiro, Per Lindmarker, Hans Johnsson, Anders Juhlin-Dannfelt and Lennart Jorfeldt

Circulation. 1999;99:1325-1330
doi: 10.1161/01.CIR.99.10.1325

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1999 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/99/10/1325

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/