

Association of Persistent Right Ventricular Dysfunction at Hospital Discharge After Acute Pulmonary Embolism With Recurrent Thromboembolic Events

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Background: In patients with acute pulmonary embolism, right ventricular dysfunction (RVD) on hospital admission is a predictor of adverse short-term clinical outcome. The aim of this study was to evaluate the prognostic value of RVD persistence at hospital discharge with regard to the likelihood of recurrent venous thromboembolism (VTE).

Methods: Echocardiography was used to assess RVD on admission and before hospital discharge in 301 consecutive patients with the first episode of acute pulmonary embolism occurring from January 1998 through July 2004. Right ventricular dysfunction was diagnosed in the presence of 1 or more of the following: right ventricular dilation (without hypertrophy), paradoxical septal systolic motion, and Doppler evidence of pulmonary hypertension. Patients were followed up at 2, 6, and 12 months and yearly thereafter. The primary end point was symptomatic, recurrent fatal or nonfatal VTE.

Results: Patients were categorized as those (1) without RVD (155 patients [51.5%]), (2) with RVD regression (RVD on admission but not at discharge; 87 patients [28.9%]), and (3) with persistent RVD (RVD on admission and at discharge; 59 patients [19.6%]). After a mean \pm SD of 3.1 ± 2.7 years, patients with RVD persistence showed an increased risk of recurrent VTE (14 patients, 9.2% patient-years) compared with those without RVD (15 patients, 3.1% patient-years) or RVD regression (3 patients, 1.1% patient-years) ($P = .001$). Six of 8 deaths related to pulmonary embolism occurred in patients with RVD persistence. At multivariate analysis, adjusted by anticoagulant treatment duration, RVD persistence was an independent predictor of recurrent VTE (hazard ratio, 3.79; $P < .001$).

Conclusion: Persistent RVD at hospital discharge after an acute pulmonary embolism is associated with recurrent VTE.

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IN PATIENTS WITH ACUTE PULMONARY embolism (PE), right ventricular dysfunction (RVD) on admission, as assessed by echocardiography, is a predictor of adverse in-hospital and 3-month clinical outcomes.^{1,2} After the acute phase of PE, RVD usually regresses,³⁻⁷ although it may persist despite treatment.^{8,9} Data about the prevalence of persistent RVD are conflicting^{6,8,9} probably because of differences in patient selection, criteria used to identify RVD, and follow-up duration. Moreover, although one study⁹ indicated that RVD persistence is a predictor of adverse long-term prognosis, it did not specifically assess the incidence of recurrent venous thromboembolism (VTE) in patients with RVD persistence compared with those without RVD or with RVD regression.

We previously showed that early echocardiographic examination is able to identify patients with increased likelihood of in-hospital adverse outcome among otherwise

“stable” (normotensive) patients with the first episode of acute PE.² The aim of the present study was to assess the prevalence of persistent RVD at hospital discharge after the first episode of acute PE and its prognostic value with regard to long-term clinical outcome. The primary end point of the study was symptomatic, objectively confirmed, recurrent fatal or nonfatal VTE.

METHODS

STUDY POPULATION

Consecutive adult patients who presented from January 1998 through July 2004 to the Emergency Department of Careggi Hospital in Florence, Italy, with the first episode of symptomatic, objectively confirmed acute PE, and survived during hospital stay, were considered for the study. Exclusion criteria were a prior documented episode of PE, chronic obstructive pulmonary disease or congestive heart failure, and the evidence at echocardiography of right ven-

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tricular hypertrophy, suggesting long-standing RVD. Patients with terminal illnesses and a life expectancy of less than 6 months were also excluded. Patients with prior DVT were not excluded from the study. However, during the initial hospitalization, we carefully assessed all patients with duplex ultrasonography to distinguish during follow-up newly occurring from preexisting DVT.¹⁰ The study complied with the Declaration of Helsinki, and all patients enrolled in the study gave a written consent.

DIAGNOSIS OF PE

The initial patient assessment included clinical history and physical examination, chest x-ray examination, 12-lead electrocardiography, arterial blood gas analysis, echocardiography, and lower-limb venous ultrasonography. The diagnosis of PE was established as previously described by perfusion lung scan and/or by spiral computed tomography; pulmonary angiography was performed as a second-line investigation in the absence of a definite diagnosis.²

ECHOCARDIOGRAPHIC EXAMINATION

Standard color 2-dimensional echocardiographic Doppler examinations were performed on admission (within 1 hour from the diagnosis of PE) and before discharge, as previously described.² The echocardiogram at discharge was performed blind to the echocardiographic results on admission, as well as to the patient's clinical history. Briefly, patients with at least 1 of the following findings were diagnosed as having acute RVD: (1) right ventricular dilation (end-diastolic diameter >30 mm or right or left ventricular end-diastolic diameter ratio >1 in apical 4-chamber view), (2) paradoxical septal systolic motion, and/or (3) pulmonary hypertension (Doppler pulmonary acceleration time <90 milliseconds or presence of a right ventricular or atrial gradient >30 mm Hg). Patients with signs of right ventricular overload in the presence of right ventricular free wall hypertrophy (end-diastolic thickness >7 mm) were excluded from the study. According to the echocardiographic features on hospital admission and at discharge, patients were classified into 3 groups: (1) patients without RVD on admission, (2) patients with RVD regression at discharge, and (3) patients with RVD persistence at discharge.

COLOR VENOUS DUPLEX SCANNING

All patients included in the study had duplex ultrasonography evaluation performed during the initial hospitalization, regardless of presence or absence of DVT symptoms. Examination was performed 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.¹¹ Pelvic and upper limb veins were routinely examined in patients with a negative lower limb scan. Venography was performed in case of indeterminate findings.

MANAGEMENT STRATEGIES

Patients were managed as previously described.² Briefly, intravenous unfractionated heparin therapy was started as soon as PE was suspected with standard doses.¹² Thrombolytic treatment (recombinant tissue-type plasminogen activator, 100 mg intravenously for 2 hours) was instituted in patients with confirmed PE in 3 different clinical contexts: (1) shock, defined as persistent systolic arterial pressure less than 100 mm Hg and clinical signs of organ hypoperfusion (clouded sensorium, oliguria, cold and clammy skin, and lactic acidosis at arterial blood gas analysis); (2) normal blood arterial pressure, RVD on ad-

mission, and delayed hemodynamic instability (defined as progression to shock and/or the need for infusion of a catecholamine [except for dopamine ≤ 5 $\mu\text{g}/\text{kg}$ per minute] and/or cardiopulmonary resuscitation); and (3) floating proximal vein thrombus after protection by temporary caval filters. After the acute phase, oral anticoagulant treatment was started and continued for at least 6 months, adjusting the dose to maintain the international normalized ratio between 2 and 3. The duration of oral anticoagulation, based on the presence of known risk factors for recurrent VTE, was independent of RVD persistence on hospital discharge and was comparable in patients with or without RVD ($P = .45$).^{12,13} After hospital discharge, patients were instructed to return for follow-up visits at 2, 6, and 12 months after discharge and yearly thereafter. The visit included medical history, clinical examination, and 12-lead ECG. All patients were educated about the main signs and symptoms of recurrent VTE and instructed to return to the study center if they noted any. Diagnostic studies for VTE recurrences were performed only in symptomatic patients.

STUDY OUTCOME AND OUTCOME MEASUREMENTS

The primary study outcome was symptomatic, objectively confirmed, recurrent fatal and nonfatal VTE. Independent experts who were unaware of patients' clinical details and of previous echocardiographic findings performed the diagnostic assessment for VTE according to a standardized procedure. The criteria for the diagnosis of recurrence of PE were a new filling defect revealed by pulmonary angiography or spiral computed tomography, or a new high-probability, unmatched perfusion defect revealed by lung scan. The criteria for the diagnosis of DVT as a recurrence of VTE in patients without DVT at baseline were the presence of a noncompressible proximal vein on ultrasonography or an intraluminal filling defect on venography. In patients with DVT at baseline, the criteria for recurrent DVT were (1) abnormal results on compression ultrasonography (proximal veins) or venography in the contralateral leg or (2) an extension of an intraluminal filling defect on venography, a newly noncompressible venous segment, or a 4-mm or greater increase in thrombus diameter (proximal veins) on ultrasonography in the ipsilateral leg.¹⁰ For patients who died in the hospital, fatal PE was defined as a fatal event that occurred in the hours after an objectively diagnosed recurrent PE or at autopsy. For patients who died at home, efforts were made to collect information concerning the cause of death. An independent expert committee, composed of 2 specialists in internal medicine and a pulmonologist (S.G., A.C., and S.V.), assessed all study outcomes. For the purpose of this study, events were not considered recurrent VTE in the absence of a definitive diagnosis.

STATISTICAL ANALYSIS

Data are expressed as mean \pm SD. The unpaired *t* test or 1-way analysis of variance was used to compare normally distributed data. The Fisher exact test was used for the comparison of noncontinuous variables expressed as proportions. Relative risks for continuous or hazard ratios (HRs) for noncontinuous variables and 95% confidence intervals (CIs) were calculated with univariate and multivariate Cox proportional hazards regression models.¹⁴ Multivariate analyses were performed with a stepwise forward regression model in which each variable with $P < .05$ or less (based on univariate analysis) was entered into the model. Survival curves were constructed according to the Kaplan-Meier method. *P* values are 2-sided, and $P < .05$ was considered statistically significant. Calculations were performed with the SPSS statistical package, version 12.0 (SPSS Inc, Chicago, Ill).

Table 1. Features of Study Patients Based on In-Hospital Course of RVD*

Features	No RVD (n = 155)	RVD Regression (n = 87)	RVD Persistence (n = 59)	Overall P Value
Age, mean ± SD, y	63 ± 17	65 ± 17	72 ± 12†	.002
Female	82 (53)	56 (64)	41 (70)	.05
Previous or concomitant disease				
Diabetes	11 (7)	6 (7)	5 (9)	.91
CVD	13 (8)	11 (13)	7 (12)	.50
Cancer	32 (21)	16 (18)	13 (22)	.84
Risk factors for VTE‡				
Permanent	27 (17)	17 (20)	17 (29)	.18
Transient	71 (46)	40 (46)	16 (27)§	.03
Idiopathic	57 (37)	30 (35)	26 (44)	.49
Symptoms and signs				
Syncope	7 (5)	14 (16)†	9 (15)†	.003
Acute dyspnea	81 (52)	64 (74)†	44 (75)†	.001
Heart rate, mean ± SD, beats/min	91 ± 20	103 ± 20†	102 ± 24†	<.001
SAP, mean ± SD, mm Hg	138 ± 18	121 ± 26†	125 ± 26†	<.001
Concomitant DVT	100 (65)	62 (71)	43 (73)	.39
Thrombolysis	12 (8)	23 (26)§	7 (12)	<.001
Vena cava filter	7 (5)	2 (2)	1 (2)	.36
Hospital stay, mean ± SD, d	13 ± 8	11 ± 6	11 ± 6	.07

Abbreviations: CVD, cardiovascular disease (previous coronary or cerebrovascular event); DVT, deep vein thrombosis; RVD, right ventricular dysfunction; SAP, systolic arterial pressure; VTE, venous thromboembolism.

*Data are presented as number (percentage) of patients unless otherwise indicated.

† $P < .05$ vs the no RVD group.

‡Risk factors for VTE were classified as permanent (deficiency of antithrombin, protein C, protein S, mutation in the factor V Leiden or prothrombin gene, the presence of lupus anticoagulants, active cancer, and immobilization from chronic medical illness) or transient (recent trauma, surgical intervention, pregnancy, and the use of oral contraceptives or hormone replacement therapy). All other patients were classified as idiopathic.

§ $P < .05$ vs the other 2 groups by Fisher exact test.

RESULTS

PATIENTS AND MANAGEMENT

Four hundred thirty-one consecutive patients with acute PE were considered for the study. Of these, 35 were excluded because of a previous documented episode of PE, whereas 73 additional patients were excluded because they were affected by chronic obstructive pulmonary disease (44 patients) and/or chronic heart failure (29 patients) or because they had echocardiographic signs of long-standing right ventricular overload (6 patients). Furthermore, 16 patients were excluded because they were not adequately examined by ultrasonography on admission, whereas 6 patients declined to participate in the study. Therefore, 301 patients were included in the study.

Patients had a mean ± SD age of 65 ± 17 years (range, 18-91 years), and 179 (59.5%) were female. In 113 patients (37.5%), PE was deemed to be idiopathic. The diagnosis of PE was obtained by lung scan in 138 patients, by computed tomography in 135, and by pulmonary angiography in 28 patients. Thirty-five patients (11.6%) showed hemodynamic impairment on admission (systolic arterial pressure <100 mm Hg).

Compared with patients without RVD, those with acute RVD on admission more often had evidence of major PE (Table 1). Patients with RVD persistence were older and less often showed transient risk factors for VTE than patients without RVD at discharge (Table 1). Of note, patients in the RVD regression group were more often treated

with thrombolytic agents than patients of the other 2 groups (Table 1). Indeed, thrombolysis was associated with a 21% absolute risk reduction for persistent RVD (95% CI, 2%-36%; $P = .03$). After the acute phase treatment, 291 (96.7%) of the 301 patients received long-term treatment with vitamin K antagonists and 10 patients (3.3%) received a vena cava filter because of permanent contraindications to anticoagulation (Table 2).

PREVALENCE AND IN-HOSPITAL COURSE OF ACUTE RVD

On admission, 146 (48.5%) of the 301 study patients had evidence of RVD. Of the remaining 155 patients (51.5%) without RVD on admission, none had evidence of RVD at hospital discharge. Of the patients who presented with acute RVD, 87 (28.9%) showed complete RVD regression at the time of discharge, whereas 59 (19.6%) retained 1 or more echocardiographic signs of RVD. Right ventricular dilation and Doppler evidence of pulmonary hypertension were the most frequently persisting signs of RVD. Paradoxical systolic motion of the interventricular septum was present in 55 (37.7%) of 146 patients with acute RVD on admission and only in 7% of them at hospital discharge.

LONG-TERM INCIDENCE OF RECURRENT VTE

Mean ± SD follow-up was 3.1 ± 2.7 years and was comparable among RVD groups (Table 2) and between patients with or without recurrent VTE (3.0 ± 2.0 and

Table 2. Follow-up Outcomes in Study Patients Based on In-Hospital Course of RVD*

Outcome	No RVD (n = 155)	RVD Regression (n = 87)	RVD Persistence (n = 59)	Overall P Value
Follow-up, mean ± SD, y	3.2 ± 2.8	3.2 ± 2.7	2.6 ± 2.6	.39
OAT duration				.30
<1 y	75 (48)	35 (40)	21 (36)	
1-2 y	34 (22)	21 (24)	20 (34)	
>2 y	46 (30)	31 (36)	18 (30)	
Recurrent VTE	15 (10)	3 (3)	14 (24)†	.001
PE-related death	2 (1)	0	6 (10)†	.001
Fatal and nonfatal PE	6 (4)	2 (2)	12 (20)†	<.001
Isolated DVT	9 (6)	1 (1)	2 (3)	.24
Death	21 (15)	11 (13)	13 (24)	.20
Malignancy	11 (8)	5 (6)	5 (9)	.76
Coronary events	2 (1)	2 (2)	0	.66
Fatal hemorrhage	2 (1)	2 (2)	1 (2)	.85
Sepsis	2 (1)	1 (1)	0	>.99
Various‡	2 (1)	0	0	.70
Undefined	0	1 (1)	1 (2)	.24

Abbreviations: DVT, deep vein thrombosis; OAT, oral anticoagulant treatment; PE, pulmonary embolism; RVD, right ventricular dysfunction; VTE, venous thromboembolism.

*Data are presented as number (percentage) of patients unless otherwise indicated.

† $P < .05$ vs the other 2 groups by Fisher exact test.

‡Includes 1 suicide and 1 end-stage renal disease.

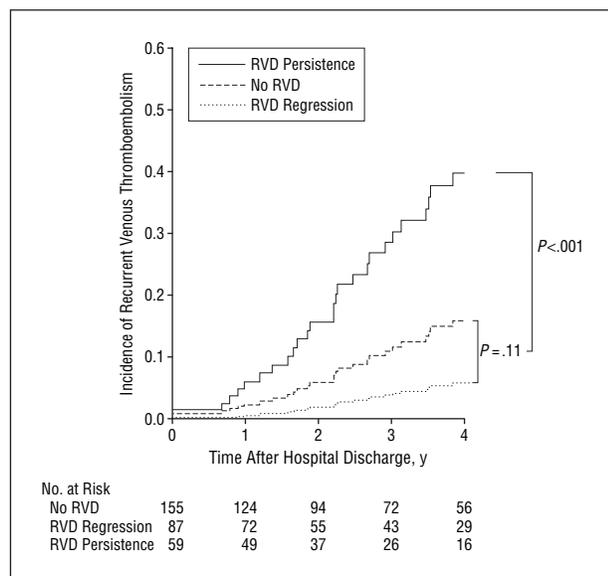


Figure. Cumulative incidence of recurrent venous thromboembolism. RVD indicates right ventricular dysfunction.

3.1 ± 2.7, respectively; $P = .83$). Patients with RVD persistence showed an increased incidence of recurrent VTE (14 patients, 9.2% patient-years) compared with both those without RVD (15 patients, 3.1% patient-years) and those with RVD regression (3 patients, 1.1% patient-years; overall $P = .001$).

Forty-five patients died (4.8% patient-years). Death was related to PE in 8 patients (7 fatal recurrent PEs and 1 death due to progressive right ventricular failure). Six of the 8 deaths related to PE occurred in patients with RVD persistence. Major bleeding events occurred in 11 patients (1.2% patient-years), all during oral anticoagulant treatment; 5 bleedings were fatal and 6 caused the cessation of treatment.

Patients with RVD persistence at hospital discharge had a significantly increased likelihood of recurrent VTE compared with those without RVD on admission or with RVD regression at discharge (HR, 2.65; 95% CI, 1.23-5.69; $P < .001$) (**Figure**). Similarly, mortality related to PE was significantly higher in patients with RVD persistence (HR, 15.18; 95% CI, 3.04-75.92; $P < .001$). When the effect of oral anticoagulant treatment duration was analyzed, patients with RVD persistence who received anticoagulants for the overall duration of follow-up had a significant reduction in the likelihood of recurrent VTE (HR, 0.17; 95% CI, 0.04-0.68; $P = .005$) compared with those not indefinitely treated.

Multivariate analysis performed using stratification by anticoagulant treatment duration (**Table 3**) showed that RVD persistence at hospital discharge was an independent predictor of recurrent VTE (HR, 3.79; $P < .001$) and death related to PE (HR, 14.01; $P < .001$). The idiopathic nature of PE was independently associated with an increased risk of recurrent VTE (HR, 2.29; $P = .03$) (Table 3). Of note, thrombolytic treatment was included in the univariate analysis as a potential predictor of recurrent VTE; however, it failed to reach statistical significance (HR, 0.31; 95% CI, 0.07-1.32; $P = .11$) and was therefore not included in the multivariate model.

COMMENT

The results of the present study show that persistence of RVD at hospital discharge is a frequent finding, occurring in approximately 20% of patients who present with a first episode of PE. These data are relevant in that the features of the present study cohort are comparable to those of other, recent PE studies,^{1,15} with elevated mean age and substantial comorbidity, and can be considered representative of PE cohorts in the real world. Our pa-

Table 3. Results of Multivariate Cox Proportional Hazards Analysis of the Relation Between Baseline Clinical Variable and Outcome*

Variables	Recurrent VTE		PE-Related Death		Death From Any Cause	
	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
RVD persistence	3.79 (1.84-7.78)	<.001	14.01 (2.78-70.34)	<.00119
Idiopathic PE	2.29 (1.08-4.86)	.037946
Malignancy8778	2.73 (1.46-5.12)	.002
Age, y9292	1.03 (1.01-1.05)†	.01

Abbreviations: CI, confidence interval; HR, hazard ratio; PE, pulmonary embolism; RVD, right ventricular dysfunction; VTE, venous thromboembolism.

*For the analysis of VTE recurrence and death related to PE, data were stratified according to oral anticoagulant treatment duration. Ellipses denote variables not included in the final model.

†Data are relative risk (95% CI) for age.

tients with acute RVD often showed some improvement during in-hospital treatment, but 1 or more echocardiographic signs were still often present at discharge, suggesting enduring right ventricular overload and/or remodeling. The 20% prevalence of persistent RVD is lower than that previously reported by others,⁹ probably because in the present study patients with previous symptomatic thromboembolic episodes, chronic lung disease, or congestive heart failure were excluded. Conversely, our prevalence of persistent RVD is greater than that reported by Pengo and coworkers¹⁵ for chronic thromboembolic pulmonary hypertension (CTPH). Indeed, persistence of RVD at discharge is not necessarily synonymous with subsequent CTPH, because delayed regression of echocardiographic signs of RVD may occur up to 30 days after PE.⁹ Moreover, the choice to reevaluate all patients before discharge (and not only symptomatic patients as in the study of Pengo and coworkers) may be a further explanation. In light of these discrepancies, however, the relationship between persistence of RVD at discharge and the occurrence of CTPH, a well-established predictor of outcome after PE,^{8,15} remains to be assessed.

Of clinical importance, our work is the first to demonstrate that patients with persistent RVD have an increased risk of recurrent thromboembolic events and death related to PE, independent of other known risk factors for recurrent VTE. Only one prior study⁹ showed that persistence of RVD at 1 year after PE was associated with an increased risk of death at 5 years. In that study, however, the different incidence of recurrent VTE between the groups with persistent RVD and RVD regression has not been reported. Of note, the present study was conducted at a single care center by a staff with substantial experience in right-sided heart echocardiography, which may limit the generalizability of the results to other institutions. Nevertheless, our data support the necessity of screening PE patients not only for acute RVD on admission^{1,2,6} but also for RVD persistence before discharge.

The relationship by which persistent RVD is associated with a high rate of thromboembolic recurrences remains unclear. The high risk of recurrence in patients with RVD persistence may be due to an underlying prothrombotic state, as well as to the hemodynamic changes associated with right ventricular overload. Consistent with the prothrombotic state hypothesis is the finding that patients with persistent RVD had a higher prevalence of per-

manent risk factors for thromboembolism, compared with patients without RVD, and more often had idiopathic PE. This finding is in agreement with the observation that patients with idiopathic PE are at increased risk of CTPH.^{15,16} The low rate of recurrence in patients with RVD regression is also of potential interest. Of note, most RVD patients (74%) showed regression of RVD despite not receiving thrombolysis. Nevertheless, thrombolytic treatment was associated with a 21% absolute risk reduction for persistent RVD, suggesting that greater long-term advantage may be achieved with aggressive treatment during the acute phase of PE. A definite answer to this controversial issue requires dedicated randomized trials.

Likewise, our findings raise the issue of whether patients with persistent RVD should receive more prolonged oral anticoagulation than patients without RVD at discharge. Our study was not powered to provide a definitive answer to this question, although it provides some potential clues regarding the optimal duration of anticoagulant treatment in these patients. We previously showed that patients with PE in general are protected from recurrence as long as they are treated with an oral anticoagulant but have high recurrence rates after withdrawal of treatment.¹⁷ In the present study, patients with RVD persistence treated with anticoagulants for the overall duration of follow-up were less likely to have VTE recurrence than patients who were treated for shorter periods. This observation emphasizes the importance of a strategy that, including persistent RVD among predictors of recurrence, might identify high-risk patients benefitting from extended anticoagulant treatment. Extending anticoagulant therapy may be particularly useful for patients with RVD persistence and idiopathic PE presentation, both representing independent risk factors for VTE recurrence in the present study. Indeed, in these patients the estimated risk of recurrence was at least 5-fold higher than that of patients without the 2 combined risk factors.

In conclusion, RVD persistence is common at hospital discharge after the first episode of PE. Following discharge, RVD persistence is associated with an increased risk of recurrent VTE and death related to PE. Patients with RVD persistence should receive a strict surveillance for recurrences. Whether reducing the incidence of RVD persistence at discharge by more aggressive treatment or extending the period of long-term anticoagulation might reduce the risk of thromboembolic recurrence should be assessed in properly designed studies.

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