

ORIGINAL ARTICLE

# Incidence of Chronic Thromboembolic Pulmonary Hypertension after Pulmonary Embolism

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## ABSTRACT

### BACKGROUND

Chronic thromboembolic pulmonary hypertension (CTPH) is associated with considerable morbidity and mortality. Its incidence after pulmonary embolism and associated risk factors are not well documented.

### METHODS

We conducted a prospective, long-term, follow-up study to assess the incidence of symptomatic CTPH in consecutive patients with an acute episode of pulmonary embolism but without prior venous thromboembolism. Patients with unexplained persistent dyspnea during follow-up underwent transthoracic echocardiography and, if supportive findings were present, ventilation-perfusion lung scanning and pulmonary angiography. CTPH was considered to be present if systolic and mean pulmonary-artery pressures exceeded 40 mm Hg and 25 mm Hg, respectively; pulmonary-capillary wedge pressure was normal; and there was angiographic evidence of disease.

### RESULTS

The cumulative incidence of symptomatic CTPH was 1.0 percent (95 percent confidence interval, 0.0 to 2.4) at six months, 3.1 percent (95 percent confidence interval, 0.7 to 5.5) at one year, and 3.8 percent (95 percent confidence interval, 1.1 to 6.5) at two years. No cases occurred after two years among the patients with more than two years of follow-up data. The following increased the risk of CTPH: a previous pulmonary embolism (odds ratio, 19.0), younger age (odds ratio, 1.79 per decade), a larger perfusion defect (odds ratio, 2.22 per decile decrement in perfusion), and idiopathic pulmonary embolism at presentation (odds ratio, 5.70).

### CONCLUSIONS

CTPH is a relatively common, serious complication of pulmonary embolism. Diagnostic and therapeutic strategies for the early identification and prevention of CTPH are needed.

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**C**HRONIC PULMONARY HYPERTENSION is considered a relatively rare complication of pulmonary embolism but is associated with considerable morbidity and mortality.<sup>1-3</sup> It is commonly believed that symptoms become manifest only several years after the initial episode of pulmonary embolism. However, the true frequency (estimated at 0.1 percent among patients who survive a pulmonary embolism) and timing are not well established, and there is limited documentation concerning predisposing factors that could be addressed in an effort to prevent this feared complication. It has been hypothesized that in situ thrombosis and pulmonary arteriopathy are common causes of vascular occlusion leading to chronic thromboembolic pulmonary hypertension (CTPH) and that pulmonary embolism is unlikely to be a common cause of this disease.<sup>4</sup>

The purpose of this prospective, long-term follow-up study was to assess the incidence of symptomatic CTPH in a large series of consecutive patients with an adequately treated episode of acute symptomatic pulmonary embolism without prior pulmonary embolism or venous thrombosis. We also evaluated potential risk factors for CTPH.

## METHODS

### SELECTION AND FOLLOW-UP OF COHORT

The University Hospital in Padua, Italy, serves as a primary referral center for patients with suspected pulmonary embolism. Patients undergo a standardized diagnostic workup.<sup>5</sup> All patients with confirmed acute pulmonary embolism were potentially eligible for but were excluded from the study if they had other diseases (e.g., systemic sclerosis or severe emphysema) that could have caused nonthromboembolic pulmonary hypertension, had preexisting exertional dyspnea, were geographically inaccessible for follow-up, or declined to participate in the study. Patients with an episode of acute symptomatic pulmonary embolism without prior pulmonary embolism or venous thrombosis were included in the cohort study, whereas patients with acute pulmonary embolism who had had a pulmonary embolism or venous thrombosis were also included in the assessment of risk factors. The institutional review board approved the study protocol, and each patient provided written informed consent.

Patients were treated with adjusted-dose unfractionated heparin, preceded in those with severe pulmonary embolism by thrombolytic drugs or, rarely,

thromboembolectomy.<sup>5-8</sup> Heparin was given as an intravenous bolus of at least 5000 IU, followed by a continuous intravenous infusion of at least 1250 IU per hour. The dose was adjusted to maintain an activated partial-thromboplastin time that was 1.5 to 2.5 times the control value. The activated partial-thromboplastin time was measured approximately six hours after the start of heparin treatment, about six hours after each measurement of the activated partial-thromboplastin time that was subtherapeutic or supratherapeutic, and otherwise daily. Oral anticoagulants were started during the first week and continued for at least six months; the target international normalized ratio (INR) was 2.0 to 3.0. The INR was usually monitored daily until the therapeutic range had been achieved, then twice or three times weekly during the first two weeks, and then once a week or less often, depending on the stability of the results. Prolongation of anticoagulant treatment beyond six months was individualized, depending on the presence of a perceived risk of recurrent venous thromboembolism.

Follow-up was performed prospectively at least every 6 months during the first 2 years and then yearly for up to 10 years. The minimal period of follow-up was one year. For patients who died during follow-up, the date and cause of death were documented. An autopsy was to be requested for any patient in whom pulmonary embolism could not be excluded as a cause of death. An independent, expert committee assessed all study outcomes.

### PROCEDURES

Patients who had otherwise unexplained persistent dyspnea on exertion or at rest during follow-up were considered to have thromboembolic pulmonary hypertension. These patients underwent transthoracic echocardiography.<sup>9</sup> If supportive findings were present, patients underwent a further diagnostic workup consisting of ventilation-perfusion lung scanning and pulmonary angiography, with direct measurement of the pulmonary-artery pressure. CTPH was considered to be present if the systolic and mean pulmonary-artery pressures exceeded 40 mm Hg and 25 mm Hg, respectively; the pulmonary-capillary wedge pressure was normal; and there was angiographic evidence of pouching, webs, or bands with or without poststenotic dilatation, intimal irregularities, abrupt narrowing, or total occlusion. Each of these findings is consistent with the presence of CTPH.<sup>10</sup> Data on all patients with suspected CTPH were reviewed by an expert

committee. The severity of symptomatic impairment was classified according to the New York Heart Association (NYHA) classification of heart failure.

#### CLASSIFICATION OF PULMONARY EMBOLISM AND RISK FACTORS

Patients were classified as having pulmonary embolism related to transient risk factors (recent trauma, fracture, surgical intervention, hospitalization, pregnancy, and the use of oral contraceptives or hormone-replacement therapy) or permanent risk factors (deficiency of antithrombin, protein C, or protein S; mutation in the factor V Leiden or prothrombin gene; and the presence of lupus anticoagulants, active cancer, immobilization from chronic medical illness, or two or more first-degree relatives with venous thromboembolism).<sup>7</sup> All other patients were classified as having idiopathic pulmonary embolism.

The following potential risk factors for CTPH were considered: age, sex, type of initial treatment, severity of the pulmonary embolism at presentation, initial presentation with idiopathic pulmonary embolism or pulmonary embolism due to permanent risk factors, concomitant symptomatic deep-vein thrombosis at presentation, and a history of venous thromboembolism. All previous episodes of pulmonary embolism and venous thrombosis were evaluated and accepted if confirmed by objective diagnostic testing<sup>6</sup> or if anticoagulant treatment had been administered for at least three months. Patients with suspected recurrent pulmonary embolism during the study underwent objective testing.<sup>5-8</sup> The severity of the pulmonary embolism at presentation was quantified by determining the remaining perfusion on the perfusion lung scan obtained at baseline.<sup>11-13</sup>

#### STATISTICAL ANALYSIS

In the cohort study, Kaplan–Meier survival estimates and their 95 percent confidence intervals were calculated to estimate the cumulative incidence of CTPH, recurrent venous thromboembolism, and mortality among patients who entered the study with a first episode of pulmonary embolism without prior venous thromboembolism. In addition, potential risk factors for CTPH were evaluated in the entire cohort with the use of univariate logistic-regression analysis. Then, all variables with a univariate level of significance of less than 0.1 were included in a backward, stepwise multivariate logistic-regression model. All calculations were per-

formed with the use of SAS software, version 6.10 (SAS Institute).

Drs. Pengo, Lensing, and Prandoni conceived the study design, oversaw its conduct, and wrote the initial protocol and first draft of the article. Drs. Prins and Marchiori contributed elements of the study design, did the statistical analysis, and helped write and revise the article. Drs. Davidson, Tiozzo, Albanese, Biasiolo, Pegoraro, and Iliceto helped design and conduct the study, interpret the data, and write or revise the article.

## RESULTS

We identified 314 consecutive patients with acute pulmonary embolism. Of these, 81 were excluded because they had conditions potentially responsible for nonthromboembolic pulmonary hypertension, preexisting exertional dyspnea, or both (38 had chronic obstructive pulmonary disease, 13 had valvular heart diseases, 5 had dilated cardiomyopathy, and 1 patient each had rheumatoid lung, left atrial myxoma, and patent ostium secundum) or because they lived too far from the study center to be followed prospectively (22 patients). Ten additional patients declined to participate in the study. Thus, 223 patients were followed (Table 1). The median follow-up was 94.3 months, and the maximum was 10 years. No patient was lost to follow-up.

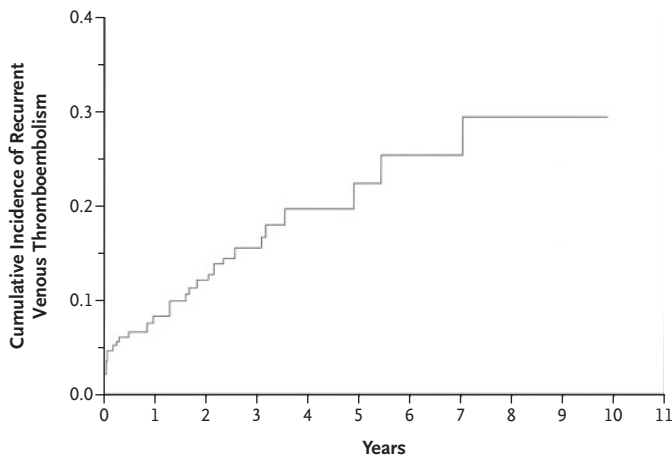
Of the 223 patients, 32 (14.3 percent) had one or more documented episodes of recurrent venous thromboembolism during follow-up. During the initial recurrence, 16 patients presented with pulmonary embolism (none of whom died) and 16 with deep-vein thrombosis only. Twenty of the 32 initial recurrences of thromboembolism (62.5 percent) occurred after the cessation of oral anticoagulant treatment. Kaplan–Meier analysis showed that the cumulative incidence of recurrent venous thromboembolism was 4.9 percent (95 percent confidence interval, 1.9 to 7.9) after 3 months, 6.5 percent (95 percent confidence interval, 3.1 to 9.9) after 6 months, 8.0 percent (95 percent confidence interval, 4.2 to 11.8) after 1 year, 22.1 percent (95 percent confidence interval, 13.5 to 30.7) after 5 years, and 29.1 percent (95 percent confidence interval, 16.9 to 41.3) at 10 years (Fig. 1).

Of the 223 patients, 18 died as a direct consequence of the acute episode, 17 on the first day and 1 on the second day after admission (case-fatality rate, 8.1 percent). During follow-up, 23 additional patients died: 12 of cancer, 5 of heart failure, 3 of

**Table 1. Demographic and Clinical Characteristics of Patients Presenting with Acute Pulmonary Embolism.\***

Characteristic	First Episode (N=223)	Previous DVT (N=58)	Previous PE (N=24)
Age — yr	60.8±17.2	62.6±17.2	61.4±15.8
Male sex — no. (%)	94 (42.2)	22 (37.9)	9 (37.5)
Risk factors for venous thromboembolism — no. (%)			
Permanent	50 (22.4)	29 (50.0)	9 (37.5)
Idiopathic	83 (37.2)	19 (32.8)	11 (45.8)
Transient	90 (40.4)	10 (17.2)	4 (16.7)
Concurrent symptomatic deep-vein thrombosis — no. (%)	83 (37.2)	14 (24.1)	6 (25.0)
Residual perfusion — %	65.8±18.6	65.1±20.0	51.7±22.0
Initial treatment — no. (%)			
Heparin alone	199 (89.2)	48 (82.8)	20 (83.3)
Thrombolysis	23 (10.3)	8 (13.8)	4 (16.7)
Surgery, vena caval filter, or both	1 (0.4)	2 (3.4)	0
Duration of anticoagulation — mo	18.5±24.0	47.0±39.3	29.2±35.1

\* Plus-minus values are means ±SD. Patients were classified as having pulmonary embolism related to transient risk factors (recent trauma, fracture, surgical intervention, hospitalization, pregnancy, and the use of oral contraceptives or hormone-replacement therapy) or permanent risk factors (deficiency of antithrombin, protein C, or protein S; mutation in the factor V Leiden or prothrombin gene; and the presence of lupus anticoagulants, active cancer, immobilization from chronic medical illness, or two or more first-degree relatives with venous thromboembolism).<sup>7</sup> All other patients were classified as having idiopathic pulmonary embolism. DVT denotes deep-vein thrombosis, and PE pulmonary embolism.



**Figure 1. The Cumulative Incidence of Recurrent Venous Thromboembolism after a First Episode of Pulmonary Embolism without Prior Deep-Vein Thrombosis.**

bleeding, 1 of myocardial infarction, 1 of stroke, and 1 of recurrent pulmonary embolism after an earlier, nonfatal recurrence. In 5 of the 12 patients who died of cancer, the cancer became clinically evident after the diagnosis of pulmonary embolism. The cumulative mortality rate was 9.4 percent (95 percent confidence interval, 5.6 to 14.2) at 2 weeks, 10.3 percent (95 percent confidence interval, 6.3 to 14.4) at 3 months, 12.5 percent (95 percent confidence interval, 8.1 to 17.0) at 6 months, 13.4 percent (95 percent confidence interval, 8.9 to 17.9) at 1 year, 20.1 percent (95 percent confidence interval, 14.2 to 26.0) at 5 years, and 25.1 percent (95 percent confidence interval, 14.2 to 36.0) at 10 years.

In 7 of the 223 patients, symptoms developed that proved to be due to CTPH (Table 2); these symptoms were preceded by a recurrent pulmonary embolism in only 2 patients. At the time of diagnosis, five patients were in NYHA class II, and two were in class III. The cumulative incidence of CTPH was 0.0 percent at three months, 1.0 percent (95 percent confidence interval, 0.0 to 2.4) at six months, 3.1 percent (95 percent confidence interval, 0.7 to 5.5) at one year, and 3.8 percent (95 percent confidence interval, 1.1 to 6.5) at two years. CTPH did not develop after two years in any of the 132 remaining patients with more than two years of follow-up (Fig. 2).

**ANALYSIS OF RISK FACTORS**

Of the 305 patients with an acute episode of pulmonary embolism who were included in the analysis of risk factors, 223 had a first pulmonary embolism, 58 had had a previous deep-vein thrombosis, and 24 had already had a pulmonary embolism (Table 1). Symptomatic CTPH developed in 3 of the 58 patients with previous deep-vein thrombosis (5.2 percent), as compared with 8 of 24 with a previous pulmonary embolism (33.3 percent). Thus, altogether, 18 patients with symptomatic CTPH could be compared with the 287 controls who did not have this complication (Table 3). The result of therapeutic anticoagulation was similar in these two groups, with a mean (±SD) INR of 2.36±0.8 among patients with CTPH and 2.39±0.8 among patients without CTPH. The INR was subtherapeutic (i.e., below 2.0) 20 percent of the time in patients with CTPH and 23 percent of the time in patients without CTPH. In the multivariate model, younger age (per decade), a previous pulmonary embolism, and a larger perfusion defect (per decile decrement in perfusion) remained significantly associated with

**Table 2. Characteristics of Patients with Symptomatic CTPH.\***

Patient No.	Age at Time of Qualifying PE <i>yr</i>	Time from Qualifying PE to Symptoms Suggestive of CTPH <i>mo</i>	Time from Symptoms to Diagnosis of CTPH <i>mo</i>	Findings at Diagnosis of CTPH			
				Mean PAP <i>mm Hg</i>	Systolic PAP <i>mm Hg</i>	Residual Perfusion <i>%</i>	NYHA Class
<b>PE as first episode of VTE</b>							
1	68	21	0	34	65	54	II
2	69	6	2	44	85	48	II
3	37	5	1	25	55	60	II
4	52	2	1	34	60	43	II
5	72	3	2	50	90	38	III
6	53	5	3	35	85	50	II
7	20	10	2	50	90	39	III
<b>Prior episode of VTE</b>							
8	66	2	0	32	85	50	III
9	17	4	3	32	60	45	II
10	53	11	0	50	85	45	III
11	32	4	0	40	70	50	II
12	65	6	6	30	57	55	II
13	41	6	8	35	55	30	III
14	32	1	0	30	45	60	III
15	76	2	2	28	50	50	II
16	22	6	6	25	45	46	II
17	53	4	8	70	120	33	II
18	50	3	5	50	85	45	II

\* NYHA denotes New York Heart Association, PE pulmonary embolism, PAP pulmonary-artery pressure, and VTE venous thromboembolism.

an increased risk of CTPH, and idiopathic presentation became significantly associated with an increased risk.

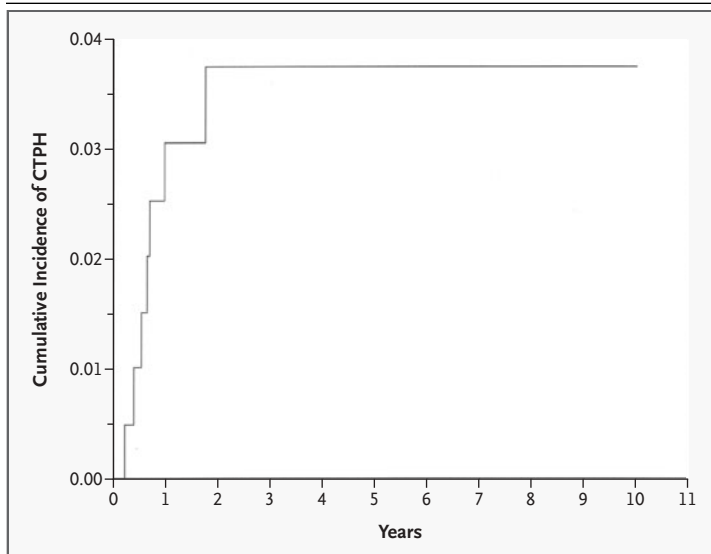
**FOLLOW-UP OF PATIENTS WITH CTPH**

Of the 18 patients with a diagnosis of CTPH, 8 underwent bilateral pulmonary thromboendarterectomy. Preoperatively, these patients had symptoms of advanced heart failure; two were in NYHA class II, four were in NYHA class III, and two were in NYHA class IV. The two patients who were in NYHA class II underwent surgery, one because of life-threatening hemoptysis, and the other because of rapidly increasing pulmonary-artery pressure. All patients had clinically significant hemodynamic improvement, and all but one were in NYHA class I after discharge. The condition of these eight patients remained stable after a median follow-up of 22

months (range, 7 to 43). In one patient, surgery was considered unsuitable owing to extensive distal obstructions. Two other patients died, and autopsy revealed extensive unresolved chronic emboli. The condition of the other seven patients remained stable (all were in NYHA class II) after a median follow-up of 38 months (range, 17 to 76).

**DISCUSSION**

We found that symptomatic CTPH affects approximately 4 percent of patients within two years after a first episode of symptomatic pulmonary embolism, with no subsequent increase in incidence. These results challenge the current belief that CTPH is rare after an episode of pulmonary embolism and occurs long after the acute episode. We attempted to minimize bias by adhering to rigorous



**Figure 2.** The Cumulative Incidence of CTPH after a First Episode of Pulmonary Embolism without Prior Deep-Vein Thrombosis.

methodologic and clinical standards. A substantial number of consecutive patients with a first episode of confirmed pulmonary embolism and without a previous deep-vein thrombosis were included in the cohort, and the median follow-up was almost eight years. Patients received state-of-the-art treatment for pulmonary embolism, and the average length of anticoagulation was more than one year. All patients with dyspnea underwent a diagnostic workup in which both recurrent pulmonary embolism and CTPH were considered. Moreover, independent experts used prespecified criteria to diagnose both recurrent pulmonary embolism and CTPH. Since symptoms of dyspnea were elicited during the routine follow-up visits, it is likely that we identified all patients with symptomatic CTPH. However, we may have missed patients with fewer symptoms and those who were asymptomatic. Hence, our estimate of the incidence of CTPH should be viewed as the lower limit. For our incidence estimates, we excluded patients who presented with recurrent pulmonary embolism or previous venous thrombosis to avoid spurious inflation of complication rates based on case finding and referral bias. We also excluded patients who had a history of other diseases that are known to be associated with pulmonary hypertension and those who had preexisting exertional dyspnea. However, we cannot exclude the possibility that the patients in whom symptomatic CTPH developed had a com-

promised pulmonary circulation before their first episode of pulmonary embolism. Taking into account these considerations, we believe that our results represent a reasonably precise estimate of the incidence of symptomatic CTPH.

The clinical course of pulmonary embolism has been described in two previous studies that followed patients for one year and six months, respectively.<sup>3,14</sup> These studies did not evaluate the incidence of CTPH but reported on the incidence of recurrent venous thromboembolism and death. Our estimates of the incidence of recurrent venous thromboembolism (8.0 percent at one year and 6.5 percent at six months) compare well with the estimates in these two studies: 8.3 percent at one year and 2.6 percent at six months, respectively. However, the mortality rate in our cohort appears lower (12.5 percent at six months and 13.4 percent at one year) than those in the other cohort studies (17 percent at six months<sup>14</sup> and 24 percent at one year<sup>3</sup>), most likely because we excluded 59 patients from our cohort who had additional cardiopulmonary abnormalities that could have interfered with the diagnosis of CTPH.

Since CTPH occurred in only a limited number of patients with acute pulmonary embolism without prior thrombotic episodes, we also included patients with acute pulmonary embolism who had had prior thrombotic episodes in the analysis of risk factors for CTPH. Among potential risk factors evaluated, multiple episodes of pulmonary embolism, a larger perfusion defect, a younger age, and idiopathic presentation of pulmonary embolism were associated with an increased risk of CTPH in the final multivariate regression model. Use of thrombolytic treatment was related in the univariate model to an increased risk of CTPH but not after adjustment for other risk factors. This is likely due to the selection of patients with extensive pulmonary embolism for this treatment. Recurrent pulmonary embolism was clearly associated with an increased risk of CTPH. However, it should be noted that some of the patients with previous episodes of pulmonary embolism had had multiple episodes that had sometimes been inadequately treated, contributing to the size of this increase in risk. However, even without the recurrence of pulmonary embolism, the risk of CTPH is not negligible but amounts to 3 to 4 percent after proper diagnosis and treatment. Obviously, changes in treatment, such as the routine use of vena cava filters or more intense anticoagulation, cannot be recommended on the basis of our

**Table 3. Risk Factors for Symptomatic CTPH.\***

Risk Factor	Patients (N=18)	Controls (N=287)	Odds Ratio			
			Univariate	95% CI	Multivariate	95% CI
Age — yr†	48.6±18.5	62.0±16.7	1.49	1.15–1.92	1.79	1.23–2.56
Male sex — no. (%)	9 (50.0)	120 (41.8)	1.39	0.53–3.61	—	—
Previous pulmonary embolism — no. (%)	8 (44.4)	16 (5.6)	16.9	5.9–48.5	19.0	4.5–79.8
Previous deep-vein thrombosis — no. (%)	3 (16.7)	55 (19.2)	0.84	0.24–3.02	—	—
Permanent risk factor — no. (%)	6 (33.3)	82 (28.6)	1.2	0.45–3.44	—	—
Idiopathic pulmonary embolism — no. (%)	10 (55.6)	103 (35.9)	2.2	0.85–5.83	5.70	1.41–22.97
Transient risk factor — no. (%)	2 (11.1)	102 (35.5)	0.23	0.05–1.01	—	—
Perfusion defect — %‡	62.6±12.9	33.7±18.6	2.1	1.6–2.9	2.22	1.49–3.31
Treatment — no. (%)						
Heparin	13 (72.2)	254 (88.5)	0.34	0.11–1.01	—	—
Thrombolysis	5 (27.8)	30 (10.5)	3.29	1.09–9.88	—	—
Surgery, vena caval filter, or both	0	3 (1.0)	—	—	—	—
Duration of anticoagulation — mo	28.8±26.8	24.5±30.7	1.0	0.99–1.02	—	—

\* Plus–minus values are means ±SD. Patients were classified as having pulmonary embolism related to transient risk factors (recent trauma, fracture, surgical intervention, hospitalization, pregnancy, and the use of oral contraceptives or hormone-replacement therapy) or permanent risk factors (deficiency of antithrombin, protein C, or protein S; mutation in the factor V Leiden or prothrombin gene; and the presence of lupus anticoagulants, active cancer, immobilization from chronic medical illness, or two or more first-degree relatives with venous thromboembolism).<sup>7</sup> All other patients were classified as having idiopathic pulmonary embolism. CI denotes confidence interval.

† In the univariate and multivariate analyses, age was considered per decade of decreasing age. This factor was included in the stepwise multivariate logistic-regression model.

‡ In the univariate and multivariate analyses, perfusion defect was considered per decile decrement in perfusion.

findings in this cohort analysis with a limited number of outcome events.

What are the clinical implications of our findings for the future management of pulmonary embolism? First, physicians should increase their awareness of the potential for CTPH in patients who present with dyspnea after a recent episode of pulmonary embolism. Second, prevention of recurrent pulmonary embolism would most likely help prevent CTPH. This could be achieved by proper diagnosis and prompt, adequate treatment of patients with pulmonary embolism, risk-factor modification (e.g., weight loss and aggressive prophylaxis in patients at risk) if possible, and the use of secondary prevention tailored as much as possible to the

risk profile of the patient.<sup>7,15</sup> For such patients, research should focus on improving the initial and long-term treatment of pulmonary embolism in order to prevent pulmonary hypertension. Perhaps attention should focus in part on achieving better anticoagulation, since it has been estimated that for vitamin K antagonists, treatment is below the therapeutic range approximately 20 percent of time, despite frequent monitoring.<sup>16-19</sup>

In conclusion, CTPH appears to be a surprisingly frequent, serious complication of pulmonary embolism, a finding that warrants confirmation. Future diagnostic and therapeutic strategies for pulmonary embolism should strive to minimize its incidence.

**APPENDIX**

Other participants in the Thromboembolic Pulmonary Hypertension Study Group were as follows: University Hospital of Padua, Padua, Italy — R. Razzolini, A. Ramondo, F. Bellotto, F. Noventa, C. Villanova, F. Barbero, D. Casara, G. Nante, D. Tormene, G. Gerosa, L. Testolin, T. Bottio; Istituto di Recovero e Cura a Carattere Scientifico, Policlinico San Matteo, Pavia, Italy — F. Piovella, M. Viganò, and A. D'Armini.

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