ARCHIVOS DE BRONCONEUMOLOGIA

Original Article

Incidence of Symptomatic and Asymptomatic Chronic Thromboembolic Pulmonary Hypertension

David Martí,[a] Vicente Gómez,[b] Carlos Escobar,[a] Carolin Wagner,[b] Celia Zamarro,[b] Diana Sánchez,[b] Allan Sam,[b] Sem Briongos,[a] Javier Gaudó,[b] Antonio Sueiro,[b] David Jiménez[b],*

[a] *Servicio de Cardiología, Hospital Ramón y Cajal, Madrid, Spain*
[b] *Servicio de Neumología, Hospital Ramón y Cajal, Madrid, Spain*

A B S T R A C T

Introduction and objectives: To assess the incidence of long-term symptomatic and asymptomatic chronic thromboembolic pulmonary hypertension (CTPH) in a cohort of patients with acute symptomatic pulmonary embolism (PE), and the potential risk factors for its diagnosis.
Methods: We conducted a prospective, long-term, follow-up study in 110 consecutive patients with an acute episode of pulmonary embolism (PE). All patients underwent transthoracic echocardiography (TTE) two years after the diagnosis of PE was made. If systolic pulmonary artery pressure exceeded 40 mm Hg and there was evidence of residual PE either by ventilation-perfusion or CT scan, patients underwent right heart catheterisation to confirm the diagnosis. In asymptomatic patients, right heart catheterisation was performed if a repeated TTE still demonstrated persistent pulmonary hypertension six months after the first.
Results: CTPH was diagnosed in 10 cases (6 patients during follow-up, and 4 at the end of the study) of the 110 patients (9.1%; 95% confidence interval [CI], 3.7-14.5). All patients had symptoms related to the disease according to a structured questionnaire. In the multivariate regression analysis, only concomitant age (relative risk [RR] 1.2 per age; 95% CI, 1.0-1.3; *P*=.03) and previous PE (RR 5.7; IC 95%, 1.5-22.0; *P*=.01) were independent predictors of CTPH.
Conclusions: The cumulative incidence of CTPH appears to be higher than previously reported. All patients had symptoms related to the disease.

Incidencia de hipertensión pulmonar tromboembólica crónica sintomática y asintomática

R E S U M E N

Introducción y objetivos: Evaluar la incidencia de hipertensión pulmonar tromboembólica crónica (HPTEC) sintomática y asintomática en una cohorte de pacientes con tromboembolia de pulmón (TEP), y las variables predictoras de su aparición.
Métodos: Estudio prospectivo de cohorte de 110 pacientes consecutivos diagnosticados de TEP en un hospital universitario terciario, y seguidos durante 24 meses. Todos los pacientes fueron sometidos a una ecocardiografía transtorácica (ETT) al final del seguimiento. En los pacientes sintomáticos con una presión sistólica pulmonar estimada (PAP) ≥ 40 mmHg se realizó un cateterismo cardiaco derecho para confirmar la HPTEC. En los pacientes asintomáticos se repitió la ETT a los 6 meses de la primera y, si la PAP se mantenía por encima de 40 mmHg, se indicó un cateterismo cardiaco.

* Corresponding author.
 E-mail address: djc_69_98@yahoo.com (D. Jiménez).

Resultados: Se confirmó HPTEC en 10 pacientes de la serie (9,1%; intervalo de confianza [IC] 95%, 3,7 a 14,5%). Todos los pacientes con HPTEC presentaron síntomas sugestivos de la enfermedad. La edad (riesgo relativo [RR] ajustado 1,2 por cada año; IC 95%, 1,0 a 1,3; p = 0,03) y el antecedente de TEP (RR 5,7; IC 95%, 1,5 a 22,0; p = 0,01) se asociaron de forma estadísticamente significativa al diagnóstico de HPTEC.
Conclusiones: La incidencia de HPTEC es más frecuente de lo descrito previamente en la literatura. La asociación entre las recurrencias tromboembólicas y la HPTEC sugiere la necesidad de optimizar la duración y la intensidad del tratamiento anticoagulante en los pacientes con TEP. No se detectaron episodios de HPTEC en pacientes asintomáticos.

Introduction

Chronic thromboembolic pulmonary hypertension (CTPH) is the most severe late-onset complication of pulmonary embolism (PE), and is characterized by the intraluminal thrombus organization and fibrous stenosis or complete obliteration of pulmonary arteries.[1] Although this is a potentially curable cause of pulmonary hypertension, its presence is associated with high morbidity. Symptoms tend to be insidious, and the diagnosis is not normally made until the disease has progressed. This limits therapeutic options and worsens prognosis.[2,3]

Previous studies have documented an accumulated incidence of symptomatic CTPH between 0.1% and 8.8% after the first episode of acute PTE,[1,4-6] and additional cases are not seen after 2 years of follow-up. This incidence could be higher for several reasons. After the first year following diagnosis of PTE, over 50% of patients have residual disease that appears in the perfusion scan or chest angio-CT scan.[7,8] Furthermore, some studies suggest that the incidence of asymptomatic CTPH is high, and that this condition is associated with a worse long-term prognosis.[9,10]

Evidence exists suggesting that persistent pulmonary hypertension following PTE precedes hemodynamic deterioration and the need for a long-term pulmonary endarterectomy,[10-12] and that the results from using this technique are better when performed earlier.[13] Therefore, the detection of CTPH in its asymptomatic phase could avoid the delay of curative surgical treatment and improve patient outcome.

The objective of this study was to perform a prospective analysis of the incidence of symptomatic and asymptomatic CTPH at 2 years of follow-up in a consecutive series of patients diagnosed with acute PTE. The aim was also to study the predictive variables for this condition.

Methods

Design

We carried out a prospective study in a cohort of patients at a tertiary university hospital between January 2003 and December 2008. The study was approved by the Local Ethics Committee and all patients gave their consent for participation.

Patients and Selection Criteria

In this study, we included all consecutive patients diagnosed with acute symptomatic PE in the emergency department of Hospital Ramón y Cajal, Madrid, Spain, with a minimum follow-up time of 2 years following the PE episode. Patients with diseases that could potentially have caused pulmonary hypertension (connective tissue diseases, chronic obstructive pulmonary disorder [COPD]; sleep apnea-hypopnea syndrome [SAHS], left heart failure, valve diseases, or human immunodeficiency virus [HIV]) were excluded from the study. The diagnosis of PE was confirmed based on the finding in the CT angiograph of a partial intraluminal defect surrounded by contrast or complete occlusion of a pulmonary artery in 2 consecutive CT scans.[14] The diagnosis of PE using ventilation/perfusion scans was performed in cases of high probability as defined by PIOPED criteria[15] (at least one segmental perfusion defect or 2 subsegmental defects with normal ventilation), or in cases of clinical suspicion of PE, inconclusive scans, and ultrasound of the legs showing a defect of venous lumen compressibility as a sign of deep vein thrombosis (DVT).

PE is considered idiopathic in the absence of the following risk factors: surgery, trauma, fracture, acute medical condition, medical immobilization for 3 or more days, air flight for over 6 hours, pregnancy, use of oral contraceptives, or an active neoplasia in the 3 months prior to diagnosis.

In the group of patients that died before finishing 2 years of follow-up, two authors (D.J. and D.M.) established the cause of death from the data from the autopsy or from the patient's attending physician.

Procedures

Patients were treated with LMWH at doses adjusted for patient weight every 12 hours for a minimum of 5 days. Vitamin-K antagonists were administered along with LMWH between the first and third days of treatment, and LMWH was interrupted when INR was stable and greater than 2.0. We monitored INR levels in accordance with the normal practices of the hospital. The attending physician determined the length of secondary prophylaxis, but this was never less than 3 months. Fibrinolytic treatment was indicated for patients in cardiogenic shock, defined as arterial hypotension (systolic blood pressure below 100 mm HG) accompanied by systemic hypoperfusion (altered mental state, oliguria, or lactic acidosis). We placed an inferior vena cava filter in patients in whom anticoagulation treatment was contraindicated. In these patients, anticoagulation was reinstated as soon as the contraindications for its use disappeared.

The study protocol did not require a transthoracic echocardiogram or heart biomarkers when acute symptomatic PE was diagnosed.

Two years after the PE episode, each patient was subjected to a questionnaire on the presence of symptoms and/or signs that would be suggestive of pulmonary arterial hypertension and a transthoracic echocardiogram (TTE). We considered the following to be symptoms and signs compatible with CTPH: persistent or progressive dyspnea following an acute thromboembolic event, right heart failure, chest pain or syncope with no other evident cause. All echocardiographic studies were performed by operators who had no other information on the clinical characteristics of the patient. We used a Vivid 7 Dimension Machine (GE Healthcare, Milwaukee, WI, U.S.A.) with a 4 MHz transthoracic transducer. Contrast methods were not used. We measured the estimated systolic pulmonary artery pressure (PAP), systolic and diastolic function of the left ventricle, valve function, and pericardial function.[16] PAP was derived from tricuspid regurgitation jet velocity (v) using a modified Bernoulli equation, where PAP (mm Hg)=$4v^2$+RAP. We obtained a higher value of v from the parasternal, apical, and subcostal windows. In order to minimize errors in measurement, we calculated right atrial pressure (RAP)

according to the diameter and inspiratory collapse of the inferior vena cava.[16] We considered pulmonary arterial hypertension to be present when PAP≥40 mm Hg.

We performed a complete etiologic study[17] on all patients with CTPH as observed by TTE, which included lung function tests, laboratory studies, abdominal ultrasound, and lung imaging tests (perfusion scans and/or CT angiography of the thorax). In symptomatic patients with criteria for pulmonary hypertension from the TTE, we performed a right heart catheterisation.[17] In asymptomatic patients with echocardiographic criteria for pulmonary arterial hypertension, we repeated the TTE at 6 months and a right heart catheterization was indicated in those patients with persistent hypertension.

Result Variables

The result variable for this study was the incidence of CTPH. This was defined as a mean pulmonary arterial pressure above 25 mm Hg (measured through the right heart catheterization) with a normal pulmonary wedge pressure (≤15 mm Hg), in the presence of segmentary perfusion defects with conserved ventilefects with conserved ventilation observed in the V/Q scan, or in the presence of occlusion, a filling defect, recanalization, bands or networks in the pulmonary arteries[18,19] as observed in the chest angio-CT scan. The final cause of the pulmonary hypertension (thromboembolic vs idiopathic) was decided by 2 researchers (D.J. and D.M.) by consensus.

Statistical Analysis

The continuous variables are expressed as mean (SD) and are compared using the Mann-Whitney U test. The categorical variables are represented as percentages and compared using the Chi-squared test, or the Fisher exact test when necessary. The statistically significant variables from the univariate analysis were included in a multivariate logistical regression analysis, applying the forward conditional method. Values of *P*<.05 were considered to be statistically significant. All statistical calculations were performed using SPSS software version 16.0 (Chicago, IL, USA).

Results

Between January 2003 and December 2005, 434 patients were diagnosed with acute symptomatic PTE at the emergency deparment of Hospital Ramón y Cajal (Figure). Twenty-seven (6%) of these were excluded for having diseases that could be responsible for pulmonary hypertension (17 cases of COPD, 8 of chronic heart failure, 1 of asthma, 1 of sleep apnea syndrome). Forty-eight patients (11%) were lost during follow-up, and 136 (31%) died within the first 2 years after being diagnosed with PE. None of the patient deaths were attributed to pulmonary hypertension. Of the 223 patients that were eligible for the study, 71 elected not to participate and 42 were excluded due to their clinical situation. The final sample size consisted of 110 patients (48 males and 62 females) diagnosed with acute symptomatic PE, who were monitored for 2 years. Six of these were diagnosed with CTPH during follow-up and the other 104 received a transthoracic echocardiogram at the end of the follow-up period.

The clinical characteristics of the patients included in the study and the treatments received are shown in Table 1. No risk factors for triggering thromboembolism were identified in 53 patients (48.2%), and 11% (12/110) had a background of PE. Three patients (2.7%) were treated with fibrinolytics and in 2 of these (1.8%), the placement of a inferior vena cava filter was indicated. Anticoagulation treatment continued for more than 6 months in 41 patients (37.6%) and 14% of patients (16/110) remained on anticoagulants during the 2 years of follow-up. Eleven cases of recurrent thromboembolism were observed during the 2 year period (8 PE and 3 DVT).
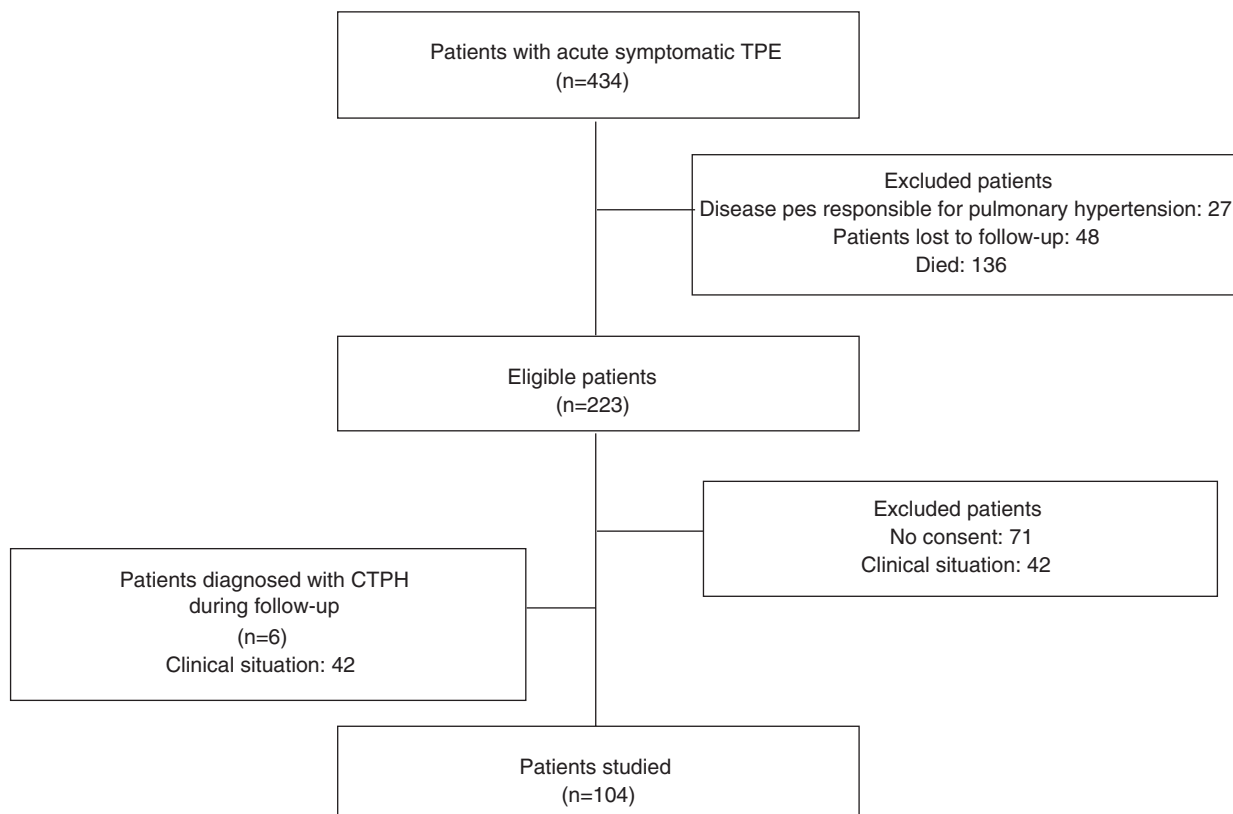
Figure. Patient flow-chart. CTPH indicates chronic thromboembolic pulmonary hypertension.

Incidence of Chronic Thromboembolic Pulmonary Hypertension

Six patients were diagnosed with symptomatic CTPH during the first two years of follow-up. We performed a transthoracic ultrasound on the other 104 patients included in the study. We identified 17 patients (16.3%) with an PAP greater than 40 mm HG and persistent thromboembolic disease in the imaging tests (chest CT angiography and/or pulmonary perfusion scan). In 10 cases, the PAP exceeded 50 mm HG, and 5 patients (4.8%) manifested symptoms indicative of CTPH. We performed a right heart catheterization in 4 of the 5 symptomatic patients, confirming CTPH in all. The ultrasound test was repeated at 6 months in 8 of the 12 asymptomatic patients. One patient died from an unknown cause and 3 were lost during follow-up. We did not detect chronic thromboembolic pulmonary hypertension in any of the 8 patients. In short, 10 patients were diagnosed with CTPH (9.1%; 95% confidence interval, 3.7-14.5), and all had symptoms attributable to the disease (Table 2).

Table 1
Baseline characteristics of the 110 patients

Variable	No. of patients (%)
Clinical characteristics	
Age >65	61 (55)
Male	55 (50)
BMI>30 kg m^{-2}	18 (16)
Risk factors for VTED	
Cancer[a]	14 (13)
Surgery	14 (13)
Immobilization ≥4 days	11 (10)
Previous PE	12 (11)
Idiopathic[b]	53 (48)
Clinical presentation	
Syncope	16 (14)
Dyspnea	72 (65)
Chest pain	59 (54)
SBP<100 mm Hg	10 (9)
O$_2$ saturation<90%	18 (16)
Heart rate≥100 bpm	35 (32)
Treatment	
Insertion of IVC filter	2 (2)
Thrombolysis	3 (3)

Abbreviations: BMI, Body mass index; IVC, inferior vena cava; PE, pulmonary embolism; SBP, systolic blood pressure; VTED, venous thromboembolic disease.

[a] Active or treated during the past year.

[b] Absence during the month previous to the PE diagnosis of: trauma, fracture, major surgery, immobilization for ≥4 days, consumption of oral contraceptives, or hormone replacment therapy.

Factors Associated with CTPH

The variables associated with the diagnosis of CTPH in the bivariate analysis are described in Table 3. Age (relative risk [RR], 1.2; 95% CI, 1.0–1.4; *P*=.009), body mass index (RR, 5.4; 95% CI, 1.4–21.3; *P*=.02), 0$_2$ saturation below 90% (RR, 2.2; 95% CI, 1.3–3.8; *P*=.03), and chest pain at the time of PE diagnosis (RR, 0.7; 95% CI, 0.5–1.0; *P*=.02) were associated with the presence of CTPH at 2 years of follow-up. After adjusting for those predictive clinical variables in the bivariate analysis, only age was significantly correlated with the appearance of CTPH at 2 years of follow-up (adjusted RR, 1.2 per year; 95% CI, 1.0–1.3; *P*=.03). When the 8 patients with objectively confirmed recurrent PTE (during the 2 years of follow-up) were grouped with the patients with a background of PE in the analysis, this variable (composed of history of PE and recurrent PE) was significantly correlated with the diagnosis of CTPH (RR, 5.7; 95% CI, 1.5–22.0; *P*=.01).

Discussion

We performed a prospective cohort study in order to determine the incidence of CTPH (symptomatic and asymptomatic) within 2 years of an acute PE episode. CTPH was confirmed in all symptomatic patients through a right heart catheterization, and the final diagnosis was made by two researchers without access to baseline information on the patient. Our study resulted in three main findings: firstly, the incidence of CTPH is greater than that described in the literature. Secondly, we did not detect CTPH in any patients that did not have any specific symptoms of the disease. Lastly, in our study, age and recurrent PE were associated with the appearance of CTPH during the 2 years of follow-up.

A precise calculation of the incidence of CTPH and the identification of factors that favor its appearance have various uses.[20] First, understanding the evolution of PE provides key information on the early natural history of CTPH, as well as the physiopathological mechanisms of pulmonary hypertension in general.[21] Second, designating populations at risk of developing CTPH would allow for early detection programs for patients in the asymptomatic phases to be implemented (e.g., using transthoracic echocardiogram or biological markers).

The incidence of CTPH in our study was superior to that previously described in the literature,[4-6,9] although the confidence intervals do overlap. Several different reasons could explain this discrepancy. First, the initial severity of PE (defined by the percentage of hypotensive and hypoxemic patients and those with tachycardia) was greater in our study. Second, previous studies analyzed cohorts of selected patients, and excluded patients with permanent risk factors,[5] background of PTE,[4,5,9] or previous exertional dyspnea.[4] In the study by Mori et al, the accumulated incidence of symptomatic CTPH was 3.8% at 2 years. Patients with a background of PE or dyspnea on exertion were excluded from this study, and sometimes

Table 2
Characteristics of CTPH patients

Patient	Sex	Age	Risk factor	Thrombolysis or IVC filter	mPAP (mm Hg)	NYHA classification
1	Female	81	Idiopathic[a]	No	45	III
2	Female	76	Previous PE	No	40	III
3	Male	79	Idiopathic[a]	No	48	III
4	Male	78	Idiopathic[a]	No	56	IV
5	Male	69	Cancer	No	40	III
6	Male	77	Immobilisation	No	50	III
7	Male	85	Idiopathic	No	43	II
8	Male	71	Idiopathic	No	31	I-II
9	Female	73	Idiopathic	No	32	I-II
10	Female	77	Previous PTE	No	49	III

Abbreviations: CTPH, chronic thromboembolic pulmonary hypertension; IVC, inferior vena cava; mPAP, mean pulmonary arterial pressureNYHA, New York Heart Association; pulmonary embolism.

[a] Patients suffered a thromboembolic recurrence that was objectively confirmed at 7, 11, and 12 months after the initial episode, respectively.

Table 3
CTPH predictors

	CTPH No.=10	No CTPH No.=100	Univariate		Multivariate	
			RR (95% CI)	P	RR (95% CI)	P
Clinical characteristics						
Age, mean (SD), y	77 (1)	62 (2)	1.2 (1.0-1.4)	.009	1.2 (1.0-1.3)	.03
Male	6 (60%)	49 (49%)	1.6 (0.4-5.9)	.51	–	
BMI>30 kg m^{-2}	5 (50%)	13 (13%)	5.4 (1.4-21.3)	.02	5.5 (1.0-31.1)	.05
Risk factors for VTED						
Cancer	1 (10%)	13 (13%)	0.7 (0.1-6.4)	.79	–	
Surgery	0	14 (14%)	–	.20	–	
Immobilization ≥4 days	1 (10%)	10 (10%)	1.0 (0.1-8.7)	1	–	
Previous PE	2 (20%)	10 (10%)	2.2 (0.4-12.1)	.34	–	
More than one episode of PE[a]	5 (50%)	16 (16%)	3.1 (1.4-6.7)	.03	5.7 (1.5-22.0)	.01
Idiopathic	6 (60%)	47 (47%)	1.7 (0.4-6.4)	.43	–	
Clinical presentation						
Syncope	2 (20%)	14 (14%)	1.5 (0.3-8.0)	.61	–	
Dyspnea	8 (80%)	64 (64%)	1.4 (0.9-2.3)	.31	–	
Chest pain	2 (20%)	57 (57%)	0.7 (0.5-1.0)	.02	0.3 (0.1-2.0)	.20
SBP<100 mm Hg	1 (10%)	9 (9%)	1.1 (0.1-9.9)	.92	–	
O$_2$ saturation<90%	4 (40%)	14 (14%)	2.2 (1.3-3.8)	.03	3.3 (0.6-19.8)	.19
Heart rate ≥100 bpm	5 (50%)	30 (30%)	2.3 (0.6-8.7)	.19		
Treatment						
Insertion of IVC filter	0	2 (2%)	–	.65	–	
Thrombolysis	0	3 (3%)	–	.58	–	

Abbreviations: BMI, body mass index; bpm, beats per minute; CI, confidence interval; CTPH, chronic thromboembolic pulmonary hypertension; IVC, inferior vena cava; PE, pulmonary embolism; RR, relative risk; SBP, systolic blood pressure; SD, standard deviation; VTED, venous thromboembolic disease.

[a] Groups the patients with a history of PE at the moment of diagnosis with those that have recurrent PE during the first 2 years of follow-up.

those with few symptoms were not evaluated. If we had not considered patients with previous PE (n=2) or patients with few symptons (n=3) in our study, the incidence of CTPH would have been 4.5%, a result consistent with the findings from Pengo et al. If we had considered the 2 patients in functional class 1 of the New York Heart Association (NYHA) as asymptomatic, the incidence of asymptomatic CTPH incidence would have been 1.8%, a comparable result to those from a previous study that evaluated the incidence of asymptomatic CTPH in patients with their first episode of PE.[9]

Other studies have shown a correlation between recurrent PE, idiopathic PE, and large perfusion defects and the appearance of CTPH.[4,5] The recurrence of thromboembolism was correlated with the appearance of CTPH in our study, but we could not demonstrate an association with idiopathic PE. We identified an elevated proportion of patients with idiopathic PE in our study (48%). This percentage could be explained by the more favorable prognosis of idiopathic PE with respect to PE secondary to cancer (with a worse prognosis and greater probability of mortality during the first two years after the diagnosis of PE). Indeed, the incidence of idiopathic PE in the initial study cohort was 39%, similar to that published by other authors.[4,22]

Our study has some limitations that must be taken into account for to interpret the results. First, the final analyzed cohort corresponds to only 49% of the patients that were initially eligible for the study, and to 25% of all PE cases diagnosed at our institution during the study period. This selection bias should be considered when analyzing the results. Second, we cannot exclude the possibility that some patients may have had CTPH when acute PE was diagnosed, which would have overestimated the true incidence of the disease. Furthermore, the high mean age of the study population could help to explain the results obtained.[23] Third, the follow-up echocardiogram was not performed by the same technician in each asymptomatic case, and so we could have underestimated the real incidence of asymptomatic CTPH. However, it would not have been ethical to subject these patients to a right heart catheterization. Lastly, we are not aware of the influence of the duration and intensity of anticoagulation treatment on the appearance of CTPH.

In conclusion, our study suggests that the incidence of CTPH is greater than that previously described in the literature. The association between recurrent thromboembolisms and CTPH indicates the need to optimize the duration and intensity of anticoagulation treatment in PE patients. Although we did not detect episodes of CTPH in asymptomatic patients, well-designed studies are needed that evaluate the effect of early detection programs on the outcome of patients who develop CTPH.

Acknowledgements

To Dr. José Luís Moya, Coordinator of the *Unidad de Diagnóstico por Imagen* (Diagnostic Imaging Unit) of the *Servicio de Cardiología* (Cardiology Department) at Hospital Ramón y Cajal.

References

1. Fedullo PF, Auger WR, Kerr KM, Rubin LJ. Chronic thromboembolic pulmonary hypertension. N Engl J Med. 2001;3:1465-72.
2. Tapson VF, Humbert M. Incidence and prevalence of chronic thromboembolic pulmonary hypertension: from acute to chronic pulmonary embolism. Proc Am Thorac Soc. 2006;3:564-7.
3. Dartevelle P, Fadel E, Mussot S, Chapelier A, Hervé P, De Perrot M, et al. Chronic thromboembolic pulmonary hypertension. Eur Respir J. 2004;23:637-48.
4. Pengo V, Lensing AW, Prins MH, Marchiori A, Davidson BL, Tiozzo F, et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. N Engl J Med. 2004;350:2257-64.
5. Becattini C, Agnelli G, Pesavento R, Silingardi M, Poggio R, Taliani MR, et al. Incidence of chronic thromboembolic pulmonary hypertension after a first episode of pulmonary embolism. Chest. 2006;130:72-175.
6. Miniati M, Monti S, Bottai M, Scoscia E, Bauleo C, Tonelli L, et al. Survival and restoration of pulmonary perfusion in a long-term follow-up of patients after acute pulmonary embolism. Medicine (Baltimore). 2006;85:253-62.
7. Nijkeuter M, Hovens MM, Davidson BL, Huisman MV. Resolution of thromboemboli in patients with acute pulmonary embolism: a systematic review, Chest. 2006;129:192-7.

8. Remy-Jardin M, Louvegny S, Remy J, Artaud D, Deschildre F, Bauchart JJ, et al. Acute central thromboembolic disease: posttherapeutic follow-up with spiral CT angiography. Radiology. 1997;203:173-80.

9. Dentali F, Donadini M, Gianni M, Bertolini A, Squizzato A, Venco A, et al. Incidence of chronic pulmonary hypertension in patients with previous pulmonary embolism. Thromb Res. 2009;124:256-8.

10. Ribeiro A, Lindmarker P, Johnsson H, Juhlin-Dannfelt A, Jorfeldt L. Pulmonary embolism: one-year follow-up with echocardiography Doppler and five-year survival analysis. Circulation. 1999;99:1325-30.

11. Stevinson BG, Hernandez-Nino J, Rose G, Kline JA. Echocardiographic and functional cardiopulmonary problems 6 months after first-time pulmonary embolism in previously healthy patients. Eur Heart J. 2007;28:2517-24.

12. De Perrot M, Fadel E, McRae K, Tan K, Slinger P, Paul N, et al. Evaluation of persistent pulmonary hypertension after acute pulmonary embolism. Chest. 2007;132:780-5.

13. Mayer E, Klepetko W. Techniques and outcomes of pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension. Proc Am Thorac Soc. 2006;3:589-93.

14. Remy-Jardin M, Remy J, Wattinne L, Giraud F. Central pulmonary thromboembolism: diagnosis with spiral volumetric CT with the single-breath-hold-technique-comparison with pulmonary angiography. Radiology. 1992;185:381-7.

15. PIOPED investigators. Value of ventilation/perfusion scan in acute pulmonary embolism: results of the prospective investigation of the pulmonary embolism diagnosis (PIOPED). JAMA. 1990;263:2753-9.

16. Otto CM. Textbook of clinical echocardiography. 2nd ed. Philadelphia: W.B. Saunders; 2000. p. 123-31.

17. Galiè N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J. 2009;34:1219-63.

18. Auger WR, Fedullo PF, Moser KM, Buchbinder M, Peterson KL. Chronic major-vessel thromboembolic pulmonary artery obstruction: appearance at angiography. Radiology. 1992;182:393-8.

19. Hoeper MM, Mayer E, Simmoneau G, Rubin LJ. Chronic thromboembolic pulmonary hypertension. Circulation. 2006;113:2011-20.

20. Jiménez D, Gaudó J, Sueiro A. Hipertensión pulmonar tromboembólica crónica. Factores de riesgo. Arch Bronconeumol. 2009;45:11-4.

21. Fedullo P, Rubin L, Kerr K, Auger W, Channick R. The natural history of acute and chronic thromboembolic disease: the search for the missing link. Eur Respir J. 2000;15:435-7.

22. White RH. The epidemiology of venous thromboembolism. Circulation. 2003;107:I4-8.

23. Saphiro BP, McGoon MD, Redfield MM. Unexplained pulmonary hypertension in elderly patients. Chest. 2007;131:94-100.