Incidence of Symptomatic and Asymptomatic Chronic Thromboembolic Pulmonary Hypertension

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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.

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Incidencia de hipertensión pulmonar tromboembólica crónica sintomática y asintomática

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 cardíaco 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 cardíaco.

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Introducción

La embolia pulmonar crónica tromboembólica (CTPH) es la complicación más grave y tardía de la embolia pulmonar (PE), y es caracterizada por la organización y estabilización del trombo intraluminal, y es el complicación tardía más severa de la embolia pulmonar (PE), caracterizada por la obstrucción o completa occlusión de una arteria pulmonar en 2 estudios consecutivos por tomografía computarizada (CT). El diagnóstico de PE se confirmó basándose en el hallazgo en el estudio de perfusión pulmonar o en el estudio de angio-CT. Los pacientes con HTEP se asociaron de forma estadísticamente significativa al diagnóstico de HTEP. Conclusión: La incidencia de HTEP es más frecuente de lo descrito previamente en la literatura. La asociación entre las recurrencias trombemboáticas y la HTEP sugiere la necesidad de optimizar la duración y la intensidad del tratamiento anticoagulante en los pacientes con TEP. No se detectaron episodios de HTEP en pacientes asintomáticos.
according to the diameter and inspiratory collapse of the inferior vena cava. We considered pulmonary arterial hypertension to be present when $PAP \geq 40$ mm Hg.

We performed a complete etiologic study 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. In asymptomatic patients with echocardiographic criteria for pulmonary arterial hypertension, we repeated the TTE at 6 months and a right heart catheterisation 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 ($\leq 15$ mm Hg), in the presence of segmentary perfusion defects with conserved ventilatory defects 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 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 $P < 0.05$ 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 department 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 an 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).
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).

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=0.009), body mass index (RR, 5.4; 95% CI, 1.4–21.3; P=0.02), O2 saturation below 90% (RR, 2.2; 95% CI, 1.3–3.8; P=0.03), and chest pain at the time of PE diagnosis (RR, 0.7; 95% CI, 0.5–1.0; P=0.02) 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=0.03). 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=0.01).

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 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,4 background of PTE,4,5 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
those with few symptoms were not evaluated. If we had not considered patients with previous PE (n=2) or patients with few symptoms (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 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.4,5

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.4,5

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 true 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.

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