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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Resumen

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 repetió 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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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. 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.1,2

Previous studies have documented an accumulated incidence of symptomatic CTPH between 0.1% and 8.8% after the first episode of acute PTE.2,3 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.11,12 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 criteria15 (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 neoplasm 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) = 4v² + 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.\textsuperscript{26} We considered pulmonary arterial hypertension to be present when PAP $\geq 40$ mm Hg.

We performed a complete etiologic study\textsuperscript{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.\textsuperscript{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 ($\leq 15$ mm Hg), in the presence of segmentary perfusion defects with conserved venterlfects 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\textsuperscript{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 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).

\textbf{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 symptomatic 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. 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. 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, 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 hypoxic 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, background of PTE, or previous exertional dyspnea. 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 3
CTPH predictors

<table>
<thead>
<tr>
<th></th>
<th>CTPH No.=10</th>
<th>No CTPH No.=100</th>
<th>Univariate RR (95% CI)</th>
<th>P</th>
<th>Multivariate RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical characteristics</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>77 (1)</td>
<td>62 (2)</td>
<td>1.2 (1.0-1.4)</td>
<td>.009</td>
<td>1.2 (1.0-1.3)</td>
<td>.03</td>
</tr>
<tr>
<td>Male</td>
<td>6 (60%)</td>
<td>49 (49%)</td>
<td>1.6 (0.4-5.9)</td>
<td>.51</td>
<td></td>
<td></td>
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<tr>
<td>BMI&gt;30 kg m(^2)</td>
<td>5 (50%)</td>
<td>13 (13%)</td>
<td>5.4 (1.4-21.3)</td>
<td>.02</td>
<td>5.5 (1.0-31.1)</td>
<td>.05</td>
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<tr>
<td><strong>Risk factors for VTED</strong></td>
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<tr>
<td>Cancer</td>
<td>1 (10%)</td>
<td>13 (13%)</td>
<td>0.7 (0.1-6.4)</td>
<td>.79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>0</td>
<td>14 (14%)</td>
<td>1.0 (0.1-8.7)</td>
<td>.10</td>
<td></td>
<td>.06</td>
</tr>
<tr>
<td>Immobilization &gt;4 days</td>
<td>1 (10%)</td>
<td>10 (10%)</td>
<td>2.2 (0.4-12.1)</td>
<td>.34</td>
<td></td>
<td></td>
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<tr>
<td>Previous PE</td>
<td>2 (20%)</td>
<td>10 (10%)</td>
<td>3.1 (1.4-6.7)</td>
<td>.03</td>
<td>5.7 (1.5-22.0)</td>
<td>.01</td>
</tr>
<tr>
<td>More than one episode of PE*</td>
<td>5 (50%)</td>
<td>16 (16%)</td>
<td>1.7 (0.4-6.4)</td>
<td>.43</td>
<td></td>
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<tr>
<td>Idiopathic</td>
<td>6 (60%)</td>
<td>47 (47%)</td>
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<tr>
<td><strong>Clinical presentation</strong></td>
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<tr>
<td>Syncope</td>
<td>2 (20%)</td>
<td>14 (14%)</td>
<td>1.5 (0.3-8.0)</td>
<td>.61</td>
<td></td>
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<tr>
<td>Dyspnea</td>
<td>8 (80%)</td>
<td>64 (64%)</td>
<td>1.4 (0.9-2.3)</td>
<td>.31</td>
<td></td>
<td></td>
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<tr>
<td>Chest pain</td>
<td>2 (20%)</td>
<td>57 (57%)</td>
<td>1.0 (0.5-10)</td>
<td>.02</td>
<td>0.3 (0.1-2.0)</td>
<td>.02</td>
</tr>
<tr>
<td>SBP&gt;100 mm Hg</td>
<td>1 (10%)</td>
<td>9 (9%)</td>
<td>1.1 (0.1-9.9)</td>
<td>.92</td>
<td></td>
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<tr>
<td>O(_2) saturation&lt;90%</td>
<td>4 (40%)</td>
<td>14 (14%)</td>
<td>2.2 (1.3-3.8)</td>
<td>.03</td>
<td>3.3 (0.6-19.8)</td>
<td>.19</td>
</tr>
<tr>
<td>Heart rate =100 bpm</td>
<td>5 (50%)</td>
<td>30 (30%)</td>
<td>2.3 (0.6-8.7)</td>
<td>.19</td>
<td></td>
<td></td>
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<tr>
<td><strong>Treatment</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Insertion of IVC filter</td>
<td>0</td>
<td>2 (2%)</td>
<td></td>
<td>.65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>0</td>
<td>3 (3%)</td>
<td></td>
<td>.58</td>
<td></td>
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</tr>
</tbody>
</table>

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.

*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.

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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**References**