Prognostic Value of Syncope in the Presentation of Pulmonary Embolism

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OBJECTIVE: Although the prognostic value of syncope has not been specifically addressed, it has generally been considered an indicator of poor prognosis in pulmonary embolism. The objective of this study was to carry out a prospective evaluation of the risk of recurrence and/or death in patients with pulmonary embolism that presents with syncope.

PATIENTS AND METHODS: A total of 168 patients had a confirmed diagnosis of pulmonary embolism. Twelve were lost to follow up and did not enter statistical analysis. The mean follow-up period was 5 months.

RESULTS: The prevalence of syncope in the patients studied was 22%. Of the 34 patients who presented syncope, objectively confirmed recurrence occurred in 2 (5.9%). In the patients who did not present syncope, recurrence was confirmed in 8 (6.6%; *P*=.8). Death occurred in 2 patients (5.9%) from the group presenting syncope and 15 (12.3%) from the remaining patients in the series (*P*=.4). The relative risk of recurrence and/or death associated with presentation of syncope was 0.5 (95% confidence interval, 0.2-1.8). A similar risk was obtained following adjustment for the presence or absence of cancer or deep vein thrombosis.

CONCLUSIONS: Patients with pulmonary embolism that presents with syncope do not have an increased risk of recurrence and/or death.

Key words: *Pulmonary embolism. Syncope. Recurrences. Death.*

El síncope como forma de presentación de la embolia de pulmón: valor pronóstico

OBJETIVO: Clásicamente se ha considerado que el síncope es un factor de mal pronóstico en la tromboembolia de pulmón (TEP), aunque esta cuestión no se ha estudiado de forma específica. El objetivo de nuestro estudio ha sido evaluar de forma prospectiva el riesgo de recurrencia y/o muerte en pacientes con síncope como forma de presentación.

PACIENTES Y MÉTODOS: Estudiamos a 168 pacientes con diagnóstico confirmado de TEP durante una media de 5 meses.

RESULTADOS: La prevalencia de síncope en la serie estudiada fue de un 22%. Entre los 34 pacientes que sufrieron un síncope, se produjo una recurrencia objetivamente confirmada en 2 pacientes (5,9%). En el resto de los pacientes se objetivaron 8 recurrencias (6,6%) (p = 0,8). Se produjeron 2 fallecimientos en el grupo de pacientes con síncope (5,9%) y 15 (12,3%) en el resto de la serie (p = 0,4). El riesgo relativo de recurrencia y/o muerte asociado al síncope fue de 0,5 (intervalo de confianza del 95%, 0,2-1,8). El riesgo fue similar después de ajustarlo a la presencia o ausencia de cáncer o de trombosis venosa profunda.

CONCLUSIONES: Los pacientes con síncope como forma de presentación de la TEP no tienen un riesgo aumentado de recurrencia y/o muerte respecto al resto.

Palabras clave: *Tromboembolia de pulmón. Síncope. Recurrencia. Muerte.*

Introduction

Pulmonary embolism has an annual incidence of 1 to 2 cases per 1000 population.[1] The rate of recurrence of correctly treated thromboembolic disease ranges from 5% to 10% per year.[2,3] As in the case of a first episode, the pathogenesis of recurrence is multifactorial, and the risk depends on both the number and severity of inherited and acquired factors.

Syncope has been described in the presentation of pulmonary embolism in between 13% and 30% of cases; however, its incidence is probably higher.[4,5] It is normally associated with massive pulmonary embolism. Greater than 50% occlusion of the pulmonary vascular tree causes right ventricular failure and impaired left ventricular filling, leading to a reduction in cardiac output, arterial hypotension, reduced cerebral blood flow, and ultimately, syncope.[6]

Another mechanism of syncope associated with pulmonary embolism is the appearance of arrhythmias associated with right ventricular overload. In a third mechanism, the embolism can trigger a vasovagal reflex that leads to neurogenic syncope.[7]

Since pulmonary emboli that present with syncope are usually massive and accompanied by acute cor

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TABLE 1
Baseline Characteristics of the 2 Patient Groups*

Variable	Without Syncope (n=122)	With Syncope (n=34)	*P*
Age, years	67.8 (15.6)	74.0 (9.8)	.03
Duration of prophylactic treatment, months	4.5 (3.5)	4.1 (3.0)	NS
Women	66	18	NS
Deep vein thrombosis	59	9	.04
Hemodynamic instability	6 (5%)	6 (18%)	.04
Prior cardiopulmonary disease	31 (25%)	6 (17%)	NS
Elevated troponin I levels	18 (15%)	18 (53%)	<.0001

*Data are shown as the mean (SD) or number of patients. NS indicates not significant.

pulmonale and hypotension,[8] syncope has been used as a criterion for inclusion in some studies of fibrinolytic therapy and mechanical thrombolysis.[9,10]

The aim of this study was to undertake a prospective evaluation of the incidence and prognostic implications of syncope in the presentation of pulmonary embolism in a consecutive series of patients diagnosed with the condition.

Patients and Methods

Patients

All patients diagnosed with pulmonary embolism in the pneumology department of Hospital Ramón y Cajal were enrolled prospectively from January 2003 to June 2004. Syncope was defined as the sudden, temporary loss of consciousness with spontaneous recuperation and without sequelae.

Treatment consisted of the use of low molecular weight heparin followed by acenocoumarol for a minimum of 3 months in the case of pulmonary embolism secondary to a transient risk factor, 6 months in idiopathic cases, and 12 months in patients with a persistent risk.[11] The use of systemic fibrinolysis was reserved for patients with a diagnosis of pulmonary embolism and hemodynamic instability.[12] Follow up was undertaken at 3-monthly intervals in all patients throughout the study. Patients received information about symptoms indicative of recurrence of pulmonary embolism or deep vein thrombosis so that they could contact a doctor associated with the study in the event of the appearance of such symptoms.

Diagnosis of Thromboembolic Disease

Deep vein thrombosis was diagnosed by ultrasound of the lower limbs according to the following criteria: visualization of an intraluminal thrombus, lack of compressibility or incomplete compressibility, and lack of spontaneous venous flow or flow following distal manipulation. Pulmonary embolism was diagnosed by spiral computed tomography (CT) or by ventilation-perfusion scintigraphy according to the criteria of the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED).[13]

Diagnosis of Recurrence

Recurrent deep vein thrombosis was diagnosed by ultrasound of the lower limbs according to the following criteria: appearance of a new noncompressible venous segment, increase of at least 4 mm in the diameter of a previously diagnosed thrombus, or visualization of a new intraluminal thrombus.[14] Recurrent pulmonary embolism was diagnosed when ventilation-perfusion scintigraphy revealed a new perfusion defect of more than 75% of a segment, or by the presence of a new intraluminal defect or the extension of a prior defect seen in spiral CT.[15]

Statistical Analysis

Time to recurrence and/or death, or the duration of follow up in patients without recurrences, was analyzed with the survival method,[16] and the relative risk of each variable was assessed via univariate and multivariate analysis in a Cox proportional hazards model. The probability of recurrence was estimated with Kaplan-Meier curves[17] and compared with the log rank test. To analyze dependence between qualitative variables we used the χ^2 test with the Fischer or Yates correction. The Mann-Whitney U test was used to compare continuous variables with a nonnormal distribution and the Student *t* test was used for normally distributed continuous variables. Statistical significance was established at $P<.05$.

Results

Between January 2003 and June 2004, 168 patients were diagnosed with pulmonary embolism. The mean age of the patients was 69 years (95% confidence interval [CI], 67-72). Twelve patients (7%) were lost during follow up. The baseline characteristics of these patients did not differ from the rest of the series. The mean period of patient follow up was 5 months (95% CI, 4.4-5.6).

Syncope was the presenting symptom of pulmonary embolism in 34 patients (22%). Pulmonary embolism was diagnosed in 84 women (18 in the group presenting with syncope and 66 in the group without syncope; 53% vs 54%; $P>.05$). The baseline characteristics of patients presenting with and without syncope are shown in Table 1.

The group containing patients who presented with syncope had a higher mean age, contained fewer patients diagnosed with deep vein thrombosis, and included a greater number of patients who presented in the emergency department with hemodynamic instability (defined by the requirement for vasopressor therapy). A greater number of patients who presented with syncope had elevated levels of troponin I.

Of the 34 patients who presented syncope, objectively confirmed recurrence occurred in 2 (5.9%). In the patients who did not present syncope, recurrence was confirmed in 8 (6.6%; *P*=.8). Death occurred in 2 patients (5.9%) from the group presenting syncope and in 15 (12.3%) from the remaining patients in the series (*P*=.4).

Table 2 shows the relative risk of recurrence and/or death in terms of age, sex, presentation of syncope, presence of deep vein thrombosis, history of cancer, troponin I levels, and need for thrombolytic treatment. When syncope was analyzed with the Cox proportional hazards model, the relative risk of recurrence or death was 0.5 (95% CI, 0.2-1.8). According to the univariate analysis, cancer presented a relative risk of recurrence and/or death of 5.6 (95% CI, 1.9-16.1) and the presence of deep vein thrombosis was associated with a relative risk of 5.3 (95% CI, 2.1-13.5).

Analysis of the Kaplan-Meier curves (Figure) revealed no differences in the rate of recurrence and/or death between patients who presented with syncope and those who did not over the course of the follow-up period (*P*=.3).

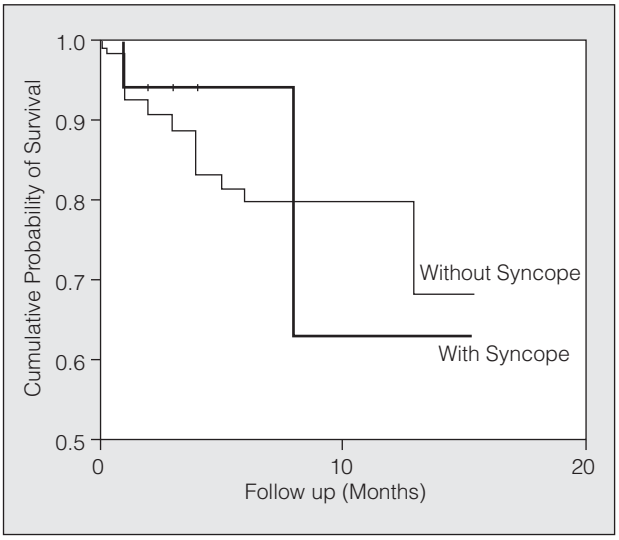

Figure. Probability of recurrence and/or death in terms of the form of clinical presentation (with or without syncope).

Discussion

Syncope is a common form of presentation of pulmonary embolism. The prevalence of syncope as an initial manifestation of pulmonary embolism in this study was 22%. Although this result is in agreement with the study of Toda et al,[19] it is higher than that found in some other studies.[18] It is quite likely that in our setting there is a high degree of sensitivity to the possibility of pulmonary embolism in patients presenting with syncope without obvious cardiac cause, whereas in earlier studies, pulmonary embolism was probably only suspected in patients in whom hemodynamic instability was maintained upon arrival in hospital. Thus, Thames et al[8] reported hypotension as a result of pulmonary embolism in 76% of patients who presented syncope, whereas in our study the figure was 18%. Our results indicate that right ventricular failure leading to low cardiac output commonly represents the transient pathophysiologic mechanism responsible for syncope caused by pulmonary embolism; it has been suggested that the heart beats themselves would be capable of fragmenting the embolism leading to decreased pulmonary vascular resistance and increased left ventricular output.[20] However, considering that not even fibrinolysis is able to dissolve more than 24% of thrombi in the first 24 hours,[21] it is possible that a significant number of cases occur in response to a transient vasovagal reflex.

Some studies have indicated the usefulness of troponin levels in the prognostic stratification of hemodynamically stable patients with pulmonary embolism.[22] This is based on the fact that acute pressure overload of the right ventricle increases the demand for oxygen in the myocardium and reduces perfusion of the right coronary artery. In this study, a greater number of patients presenting with syncope also had elevated levels of troponin I, a finding that supports acute right ventricular failure as a cause of syncope. However, in the univariate analysis we found no association between elevated levels of troponin I and the risk of death or recurrence of pulmonary embolism. Our results indicate that while patients with pulmonary embolism and syncope more commonly present right ventricular failure and elevated levels of troponin I, this failure is transient and does not increase the risk of recurrence or death.

Deep vein thrombosis was significantly more common in patients who did not present syncope. It can be postulated that the entire thrombus is embolized in patients without deep vein thrombosis and that acute right ventricular overload or a transient vasovagal response is more likely. In the multivariate analysis, the presence of deep vein thrombosis was associated with greater risk of recurrence and/or death. Various studies have demonstrated that residual deep vein thrombosis is associated with an increased risk of recurrence.[23,24] Our results confirm that the absence of deep vein thrombosis in ultrasound of the lower limbs equates with a lower risk of recurrence of embolism.

TABLE 2
Relative Risk of Recurrence and/or Death According to Baseline Characteristics*

Characteristic	Univariate RR (95% CI)	Multivariate RR (95% CI)
Age	1.0 (0.9-1.0)	–
Sex	1.5 (0.6-3.6)	–
Elevated troponin I levels	0.7 (0.2-2.2)	–
Syncope	0.5 (0.2-1.8)	1.1 (0.2-5.0)
Presence of deep vein thrombosis	5.3 (2.1-13.5)	6.4 (1.8-22.2)
Cancer	5.6 (1.9-16.11)	3.9 (1.3-11.8)
Requirement for fibrinolytic treatment	0 (0-230)	–

*RR indicates relative risk; CI, confidence interval.

In agreement with a recent study by Cushman et al,[25] we found that cancer acts as an independent negative prognostic factor in patients with thromboembolic disease. These patients should receive secondary prophylactic treatment on an ongoing basis. It remains to be determined whether maintenance of primary prophylactic treatment is effective in this subgroup of patients.[26]

Our results demonstrate that syncope in the presentation of pulmonary embolism does not imply an increased risk of death and/or recurrence. While all patients in our series received conventional treatment,[12] thrombolytic treatment was reserved for those patients who were hemodynamically unstable. In our study group, low molecular weight heparin was equally safe and effective in those patients who presented syncope as in those who did not.

In summary, syncope is a common form of presentation of pulmonary embolism. Patients who present with syncope do not have an increased risk of death and/or recurrence. The treatment and the duration of secondary prophylactic therapy in general use is not associated with poor prognosis in patients in whom pulmonary embolism presents as syncope.

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