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Chronic thromboembolic pulmonary hypertension. Clinical characterization, hemodynamics, and survival

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ABSTRACT. Background: Although average survival in chronic, major vessel, thromboembolic pulmonary hypertension (CTPH) has been estimated in the vicinity of 2.5 to 3 years from diagnosis, the natural history of patients has not been clearly elucidated. The aim of the present study is to characterize mortality in a Mexican population of patients with CTPH and to investigate factors associated with their survival. **Methods:** Retrospective clinical review of a dynamic cohort of fifteen patients with CTPH, mean (SD) age of 48 (16) years, enrolled between 1979 and 1989 and followed through May 1994 in a tertiary referral center. Diagnosis of CTPH was established in the basis of: 1) demonstration of pulmonary arterial hypertension and cor pulmonale, 2) no evidence of primary heart and/or lung disease, 3) the presence of lobar or at least segmental defect (s) in the lung scan, 4) confirmation of perfusion defects by pulmonary angiogram. Measurements included hemodynamic and functional variables in addition to information on demographic data and medical history. All these patients received long-term oral anticoagulation for treatment. As an index for determining survival we used the initial diagnostic catheterization. **Results:** Mean (SD) baseline hemodynamic values were: mean pulmonary artery pressure 6.93 (2.13) kPa; cardiac index 3.09 ± 0.81 $L \bullet min^{-1} \bullet m^2$, and calculated pulmonary vascular resistance of 921 $dynes \bullet sec \bullet cm^5$. The right ventricular end-diastolic pressure was 1.73 (0.79) kPa. The estimated median survival of the group was 2.16 years (95% CIs; 0.08 to 5.91 years) which is statistically different from the 3.12 years (95% CIs; 0.5 to 13.25 years) median survival of adult patients with primary pulmonary hypertension also followed at our institution (Chi^2 log rank = 10.03, $p < 0.0015$). Except for female gender (hazard ratio: 0.08), and a decreased arterial oxygen content (hazard ratio: 13.9), none of the other demographic, clinical, functional, and hemodynamic variables was significantly associated to mortality (Cox's proportional hazards model). **Conclusions:** Despite medical treatment, patients with CTPH have a poor survival expectancy which appears to be worse than that of adult patients with primary pulmonary hypertension.
Key words: *Pulmonary circulation, pulmonary hypertension, pulmonary thromboembolism.*

RESUMEN. A pesar de que el promedio de sobrevida en la hipertensión arterial pulmonar crónica secundaria a tromboembolia pulmonar no resuelta (TEPC), ha sido estimada en cerca de 2.5 a 3 años desde el diagnóstico, la historia natural de los pacientes no ha sido claramente establecida. El propósito del presente estudio es caracterizar la mortalidad en una población de pacientes mexicanos con TEPC e investigar los factores asociados con su sobrevida. **Métodos:** Revisión clínica retrospectiva de quince pacientes con TEPC, edad media 48 ± 16 años, admitidos en un hospital de tercer nivel entre 1979 y 1989, dándoles seguimiento hasta mayo de 1994. El diagnóstico de TEPC fue establecido con las siguientes bases: 1) Demostración de hipertensión arterial pulmonar y *cor-pulmonale*. 2) No evidencia de enfermedad primaria de corazón y/o parenquimatosa pulmonar. 3) La presencia de defecto (s) lobar o al menos segmentario en el estudio de gammagrafía pulmonar perfusoria de pulmón. 4) Confirmación de defectos de perfusión por angiografía pulmonar. Se efectuaron mediciones de variables hemodinámicas y funcionales respiratorias, además de información sobre datos demográficos e historia clínica. Todos los pacientes recibieron tratamientos a largo plazo con anticoagulantes orales. Como un indicador para determinar la sobrevida se usó el resultado del cateterismo derecho diagnóstico inicial. **Resultados:** Los valores hemodinámicos basales fueron media (DS): presión arterial pulmonar media 6.93 (2.13) Kpa, índice cardiaco 3.09 ± 0.81 $L.min^{-1}.m^2$ y resistencia pulmonar vascular calculada de 921 $dinas.seg.cm^5$. La presión diastólica final del ventrículo derecho fue 1.73 (0.79) Kpa. La sobrevida media estimada del grupo fue de 2.16 años (95% cls; 0.08 a 5.91 años), lo cual es estadísticamente diferente de los 3.12 años (95% cls; 0.5 a 13.25 años) sobrevida media de los pacientes adultos con hipertensión pulmonar primaria también estudiados en nuestra institución (Chi^2 log rank = 10.03 $p < 0.0015$). Exceptuando al factor sexo femenino (proporción de riesgo de 0.08); y a la disminución del contenido de oxígeno arterial (proporción de riesgo 13.9) ninguna de las otras variables demográficas, clínicas, funcionales y hemodinámicas fueron significativamente asociadas a la mortalidad. (Modelo, de riesgos, proporcional de Cox). **Conclusiones:** A pesar el tratamiento médico, los enfermos con TEPC tienen una expectativa probre de sobrevida, la cual parece ser más mala que la de los enfermos adultos con hipertensión arterial pulmonar primaria.
Palabras clave: *Circulación pulmonar, hipertensión arterial pulmonar, tromboembolia pulmonar crónica.*

INTRODUCTION

Chronic, major vessel thromboembolic pulmonary hypertension (CTPH) is now a well recognized and relatively rare clinical entity for which the pathogenesis remains unclear. It has been suggested that in many patients the

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emboli arise from sites of venous thrombosis in the deep venous system of the legs; more rarely, they arise from indwelling venous devices or from venous thrombosis of the major upper extremity veins. These emboli lodge in the pulmonary circulation and for reasons still unclear, do not resolve completely, rather, in the course of months or years they follow an aberrant pathway of organization, incomplete recanalization and finally, they are incorporated into the vascular wall remaining as obstructing lesions in the main, lobar, segmental and sub-segmental arteries, leading eventually to pulmonary hypertension and cor-pulmonale.[1-4]

As the pathogenesis, the natural history of these patients has not been clearly defined. Most of these patients present with evidence of severe clinical and hemodynamic deterioration at diagnosis. The average survival from the time of diagnosis until death has been estimated in the vicinity of 2.5 to 3 years.[2] In recent years, pulmonary thromboendarterectomy (PT) has been shown to be a successful therapeutic approach for this disease[4-8] and at present most patients undergo this modality of treatment. Under these circumstances, it would be difficult to obtain more information regarding the natural history of patients with this condition.

Pulmonary thromboendarterectomy has been performed at our institution since 1991.[8] Prior to this, most of our patients with CTPH were treated only with formal oral long-term anticoagulation. Accordingly, these patients represent a suitable population to learn about the natural history of this condition and to evaluate the future impact of an still high risk procedure such as PT. Therefore, the aim of this study is to describe the clinical, functional and hemodynamic characteristcs of a group of patients with CTPH, to characterize their mortality and to investigate factors associated with survival.

METHODS

Patients. The medical records of 450 consecutive patients who were admitted to the Cardiopulmonary Department of the National Heart Institute of Mexico City between 1978 and 1991, and who met the criteria for pulmonary arterial hypertension (PAH) and cor pulmonale[9] were reviewed. As part of the protocol for the study of their PAH, most of these patients had had a thorough evaluation including: medical history and physical examination, laboratory test, chest X-ray, electrocardiogram (EKG), echocardiogram, pulmonary function tests (PFT's), ventilation/perfusion (V/Q) lung scan and finally, right heart catheterization. The methodology for right heart catheterization has described elsewhere.[10,11] From this population of PAH patients, we selected 21 cases as having chronic thromboembolic obstruction of the major pulmonary arteries as the cause of their pulmonary arterial hypertension. Definitive diagnosis of CTPH was made according to the following criteria: 1) Demonstration of pulmonary hypertension and cor-pulmonale. 2) No evidence for primary heart and/or lung disease. 3) The presence of lobar or at least segmental perfusion defect (s) in the lung scan (anterior, posterior, and left and right anterior obliques views) that were mismatched to the ventilation scan. 4) Confirmation of above perfusion defects by the pulmonary angiogram. To be included in this study on natural history, the follow-up of the patients had to be available. Six patients were excluded; 5 of them because they had a pulmonary thromboendarterectomy done for treatment, and one as a result of lost to follow-up.

In the 15 remaining patients the diagnosis of chronic pulmonary thromboembolism was initially made between 1979 and 1989 and the management with long-term anticoagulation had been accordingly established. The patients were followed for survival and treatment at our outpatient clinic at regular intervals until May 1994, and the doses of acenocoumarin were adjusted to maintain a therapeutic range (equivalent to an INR of 2.0 to 3.0).

Analysis. In the present study: 1) we analyzed the demographic, clinical, functional, and hemodynamic characteristics of the patients at diagnosis. 2) For the survival analysis we used the initial diagnostic catheterization as an index for determining survival. The method of Kaplan-Meier was used to estimate overall survival distribution. 3) Univariate analysis based on the proportional hazards model, was used to examine the relationship between survival and selected demographic, medical-history, pulmonary-function, laboratory, and hemodynamic variables measured at initial catheterization. Upon completion of the univariate analysis and after adjusting for age of the patients, any related variable with a p-value < 0.25 was considered as a candidate for the multivariate model. Multivariate analysis based on the Cox proportional hazards regression analysis was used to examine the adjusted independent effect on survival of each variable, controlling for possible confounders. For both the survival analysis and the proportional hazards models we used STATA software.[12] Results are expressed as hazards ratios with 95% confidence intervals (CIs). For the rest of the statistical analysis we used paired and unpaired t test. All values are expressed as mean ± one standard deviation (SD).

RESULTS

Demographic characteristics. The mean (SD) age of the patients is 48.2 (16) years and women (n = 9) are predominant. The overall female-to-male ratio was 1.5:1. All patients are Hispanic. Nine out of the 15 patients were born, raised and are residents of Mexico City (2,240

meters above sea level). The rest of the patients have been referred to us from different parts of the country.

Medical history. A past history for deep venous thrombosis (DVT) and/or a history of previous acute pulmonary embolism (PE) was present in 36% and 40% of the patients respectively. Thirteen percent of the women at reproductive age (2/15) had taken oral contraceptives at some time and there were 2.26 live births per female patient in the same population. Four patients were previous or current cigarette smokers but there was no any clinical and functional evidence of chronic obstructive pulmonary disease in them. Other associated diagnosis included: Obesity (2), and diabetes mellitus (1), and systemic arterial hypertension (3).

Symptoms and physical findings. The frequency of symptoms at diagnosis (initial catheterization) was as follows: dyspnea (100%); chest pain (66.6%); orthopnea (46.6%); paroxysmal nocturnal dyspnea (26.6%); syncope or near syncope (26%); and hemoptysis (20%). The mean (SD) time from onset of the first symptom until the diagnosis of CTPH was 3.07 (2.87) years (range: 1 month to 10 years). The functional status of the patients at diagnosis according to the New York Heart Association (NYHA) classification was as follows: None of the patients were in class I, 20% in class II, 60% in class III, and 20% of the patients were in class IV. The physical findings of the CTPH patients were those usually found in any patient with pulmonary hypertension. An increase in the pulmonic component of the second heart sound (P2) was reported in all cases. A soft systolic pulmonic murmur was found in 33% of the patients. Tricuspid regurgitation was noted in 40% and pulmonic insufficiency in 33% of the patients. A continuous murmur over the lung fields accentuated during inspiration was reported in three of the patients. Peripheral edema was present in 60% of the patients, and hepatomegaly and cyanosis were noted in 73% and 40% respectively.

Diagnostic studies. The chest X-ray (PA film) showed the typical changes associated with pulmonary hypertension namely; prominence of the main pulmonary artery and enlarged hiliar vessels in all cases. The mean (SD) diameter of the right main pulmonary artery at the pars-interlobaris was 19.7 (1.9) (normal = < 16 mm), and the mean PL/T (pulmonary lobar diameter/maximum transverse diameter of the thorax) index was 40 (5) (normal = < 38%).[13] The mean cardio-thoracic index of the group was 55 (4) %. None of the patients had pleural effusion. The electrocardiogram showed a sinus rhythm and evidence of right ventricular hypertrophy in all cases. Signs of right ventricular strain (i.e. T-wave inversion with or without ST depression in right precordial leads)[14] were present in 86% of the patients. The echocardiogram, confirmed right ventricular hypertrophy and showed variable degrees of right ventricular dilatation. Systolic left ventricular function was considered normal in all cases. The mean (SD) left ventricular ejection fraction was 59 (12) %.

Results of selected pulmonary function variables are shown in *table 1*. In most of the patients lung volumes were normal. There was evidence of mild pulmonary restriction (i.e. VC and TLC < 80% of predicted) in four patients, and airway obstruction (FEV1/FVC < 70%) was also present in four. None of these patients was a cigarette smoker. Mild to moderate hypoxemia was present in all of the patients and hypocapnia existed in all but two patients. Mean (SD) normal values for Mexico city are: PaO_2 = 8.99 (0.33) kPa; $PaCO_2$ = 4.66 (0.33) kPa.[15] The dead space (Vd/Vt) as well as total shunt (Qs/Qt) were increased in all but one patient. Diffusing capacity for carbon monoxide was not measured. The mean (SD) hemoglobin and hematocrit levels of the group were 160 (25) g/L, and 0.49 (0.074) % respectively. Antinuclear antibody was positive at low titers in only one of the patients and the total platelet count was normal.

The perfusion defects found in the perfusion/ventilation lung scan were as follows: lobar single defect confined to one lung in 11% of the cases, unilateral multiple lung perfusion defects in 33%, and bilateral multiple lung perfusion defects in 56% of the patients. Pulmonary angiogram confirmed proximal vascular abnormalities of the major pulmonary arteries including: abrupt vascular narrowing and complete vascular obstruction, “pouching” defects, webs or bands with and without poststenotic dilatation. Most of these abnormalities were bilateral.

Hemodynamic findings. Selected hemodynamic variables in CTPH patients at the time of initial diagnostic catheterization are summarized in *table 1*. The patients as a group, had severe pulmonary arterial hypertension. Mean (SD) baseline hemodynamic values were as follow: mean pulmonary arterial pressure (PAP) was 6.93 (2.13) kPa (range 3.86 to 11.33), mean right atrial pressure (RAP) 1.19 (0.62) kPa (range 0.45 to 2.9), and right ventricular end-diastolic pressure (RVEDP) of 1.71 (0.79) kPa (range 0.76 to 3.73). The mean pulmonary capillary wedge pressure (PCWP) was 1.53 (0.87) kPa (range 0.37 to 3.19). The mean cardiac index (CI) was 3.09 (0.81) L. $min^{-1}.m^2$ (range 1.65 to 4.3) and the mean calculated pulmonary vascular resistance (PVR) was 921 (590) dynes.sec.cm^{-5}. Mean systemic arterial pressure (MAP) was 13.72 (2.26) kPa (range 11.06 to 15.99). An elevated PCWP (> 1.99 kPa) was found in 33.3% of the patients in the presence of normal left ventricular systolic function as assessed by echocardiogram. Also, patients with orthopnea had a significantly ($p < 0.01$) higher PCWP (2.4 (0.66) kPa) than their counterparts without this presenting symptom (0.93 (0.39) kPa). Pulmonary vascular resistance was not modified by oxygen brea-

Table 1. Pulmonary function variables and hemodynamic findings at entry into study.

Variable	Mean (SD)
Age (years)	48.2 (16)
Sex (Male/Female)	6/9
VC % predicted	83 (25)
TLC % predicted	79 (11)
FEV1 % predicted	74 (24)
FEV1/FVC %	76 (11)
Arterial PO_2. kPa	6.93 (0.8)
Arterial PCO_2, kPa	3.99 (0.8)
Arterial pH	7.46 (0.05)
Vd/Vt %	0.47 (0.09)
Qs/Qt %	9.75 (3.8)
(a-v)DO_2 vol %	5.7 (2.3)
Hct %	49.4 (7.4)
MAP, kPa	13.72 (2.26)
RAP, kPa	1.22 (0.62)
RVEDP, kPa	1.71 (0.77)
PAP, kPa	6.93 (2.13)
PCWP, kPa	1.53 (0.87)
PAd-PCWP, kPa	2.67 (1.59)
CI $L.min^{-1}.m^2$	3.09 (0.81)
PVR dynes-sec-cm^{-5}	921 (590)
LVEF %	59.3 (12)

Abbreviations: VC: Vital Capacity; TLC: Total Lung Capacity; FEV1 Forced Expiratory Volume in one second; FVC: Forced Vital Capacity; Vd/Vt: Physiologic Dead Space; Qs/Qt: intrapulmonary shunt; (a-v)DO_2: arterial-venous oxygen content difference; Hct: hematocrit; PO_2 Oxygen Pressure; PCO_2: Carbon Dioxide Pressure; MAP: Mean Systemic Arterial Pressure; RAP: Right Atrial Pressure; RVEDP: Right Ventricle End Diastolic Pressure; PAP: Mean Pulmonary Artery Pressure; PCWP: Pulmonary Capillary Wedge Pressure; PAd: Pulmonary Artery Diastolic Pressure; CI: Cardiac Index; PVR: Pulmonary Vascular Resistance; LVEF: Left Ventricular Ejection Fraction.

thing in the group as a whole (PVR before: 909 (490), after: 842 (520) dynes.sec.cm^{-5}, p = n.s.).

Survival. As in May of 1994, 14 out of the 15 CTPH patients died at a mean (SD) of 2.63 (2.2) years from diagnosis. Right heart failure either alone (12/14), or combined with other events (gastrointestinal bleeding: 2.) was the leading cause of death. *Post mortem* studies were performed in two out of five patients who died in the hospital. This study confirmed the existence of significant obstruction of the main pulmonary arteries by organized thrombi in both cases. Only 3 patients survived more than 5 years from diagnosis and only one of the 15 patients is still alive after 4.41 years.

Summary statistics on survival and length of follow-up for the 15 evaluable patients are shown in *figure 1*. For comparison, the survival of CTPH patients is compared to that of 42 adult patients with primary pulmonary hypertension (mean age = 28 (9) years old) also followed at our institution.[16] The median survival for the whole CTPH patients group was 2.16 years (95% CIs; 0.08 to 5.91 years) which is statistically different from the 3.12 years median survival (95% CIs; 0.5 to 13.25 years) of the patients with primary pulmonary hypertension (Chi^2 log rank = 10.03, $p < 0.0015$). In order to assess the adjusted independent effect of age and diagnosis on survival we performed a separate multivariate analysis (Cox's proportional hazards model) combining patients from both series (n = 57). In this analysis, CTPH diagnosis was significantly associated to mortality (hazard ratio = 4.73; $p < 0.002$) whereas age was not associated (hazard ratio = 0.98; p = 0.22).

Factors associated with survival in CTPH (Univariate and multivariate Analysis). Using single-variable cox models, none of the demographic, clinical, functional, and hemodynamic variables at entry were significant predictors of mortality. After adjusting for age of the patients, an increased physiological dead space (hazard ratio: 5.43) was the only significant variable associated with mortality. Also, although not statistically significant, female gender (hazard ratio: 0.23) had a protective effect against the risk of death whereas NYHA class IV (hazard ratio: 4.35), a decreased PaO_2 (hazard ratio: 2.08), and a decreased arterial oxygen content (hazard ratio: 3.85) were all associated with an increased risk of death *(Table 2)*. Next, the

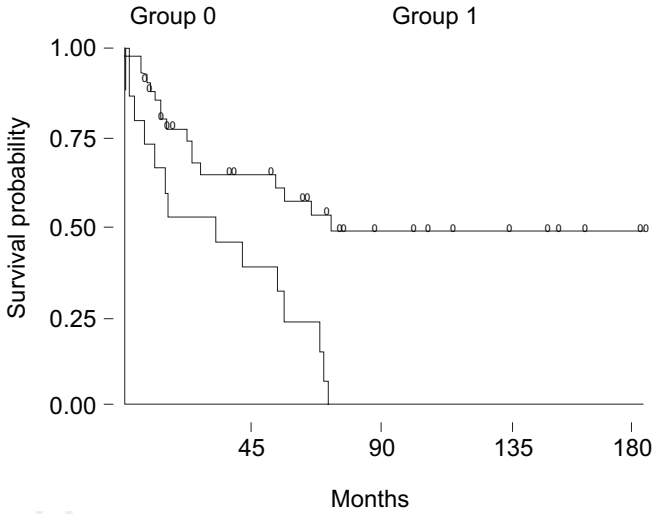

Figure 1. *Survival in Chronic Thromboembolic Pulmonary Hypertension. Kaplan-Meier survival estimates in patients with CTPH (1) are compared to those of adults with Primary Pulmonary Hypertension[16] (0). Median survival estimates are 2.16 years (95% CIs; 0.08 to 5.91 years) and 3.12 years (95% CIs; 0.05 to 13.25 years) respectively (Chi^2 log rank = 10.03, p < 0.0015).*

Table 2. Analysis relating survival time to age- adjusted selected baseline variables.

Variable	Hazard Ratio (95% CI)	p
Demographic data		
Sex (women)	0.23 (0.05 to 1.14)	0.06
NYHA functional class (IV vs II and III)	4.35 (0.48 to 39.2)	0.17
Peripheral edema	1.46 (0.38 to 5.62)	0.54
Syncope	1.29 (0.38 to 4.32)	0.65
Paroxysmal Nocturnal Dyspnea	1.55 (0.39 to 6.08)	0.49
Orthopnea	1.82 (0.44 to 7.54)	0.37
Pulmonary Function Tests		
VC % predicted (< 80%)	0.43 (0.09 to 1.96)	0.26
FEV1 % predicted (< 80%)	0.67 (0.18 to 2.51)	0.53
Vd/Vt % (> 0.47)	5.43 (1.03 to 28.4)	0.04
Arterial PO_2, kPa (< 6.93)	2.08 (0.57 to 7.57)	0.24
CaO_2 Vol % (< 17 vol %)	3.85 (0.72 to 20.5)	0.10
CvO_2 Vol % (< 11.5 vol %)	2.01 (0.52 to 7.77)	0.28
Hemodynamic Variables		
RAP, kPa (> 1.19)	0.44 (0.09 to 2.08)	0.27
RVEDP, kPa (> 1.66)	0.74 (0.19 to 2.75)	0.63
PAP, kPa (> 6.93)	0.84 (0.18 to 3.83)	0.81
MAP, kPa (< 13.72)	1.01 (0.93 to 1.11)	0.59
PCWP, kPa (> 1.53)	2.89 (0.28 to 29.9)	0.33
CI L.min.m^2 (< 3 L.min.m^2)	0.59 (0.11 to 3.14)	0.50

Abbreviations: NYHA: New York Heart Association functional class; CaO_2: arterial oxygen content; CvO_2: mixed venous oxygen content. Rest of abbreviations as in *table 1*.

proportional hazards model was used in multivariate analysis. Any variable in *table 2*, whose value was p < 0.25 was considered as a candidate for the multivariate model, as the use of a more traditional level (such as 0.05) often fails to identify variables known to be important.[17,18] When all these variables were confronted alltogether, female gender (hazard ratio: 0.08), and a decreased arterial oxygen content (hazard ratio: 13.9) remained significantly associated to mortality. The adjusted hazard ratios and their 95% CIs are shown in *table 3*.

Table 3. Multivariate analysis relating mortality to selected variables.

Variable	Hazard Ratio (95% Confidence Interval) Regression 1 +	p <
Age	0.96 (0.91 to 1.01)	0.14
Sex	0.08 (0.006 to 0.98)	0.049
NYHA	2.28 (0.21 to 24.9)	0.45
Vd/Vt	1.84 (0.25 to 13.19)	0.49
CaO_2	13.9 (1.17 to 165)	0.039
PaO_2	0.67 (0.10 to 4)	0.64

NYHA indicates New York Heart Association functional class; Vd/Vt, physiological dead space; CaO_2, arterial oxygen content.
+ Log likelihood = - 19.256; χ^2 (6) = 13.27, p< 0.039.

DISCUSSION

Chronic thromboembolic pulmonary hypertension (CTPH) is a term proposed by Moser KM, et. al. to describe a severe and progressive form of pulmonary hypertension that, although rare, may occur after an aberrant course of pulmonary embolism.[1-3,5-7,20-22] CTPH represented approximately the 5% (21/450 pts) of all forms (primary and secondary) of PAH seen at our department between 1978 and 1991. The potential for definitive treatment and improved recognition, however, have increased the number of patients with this condition in recent years and questions regarding the natural history of the disease and the impact of a still risky surgical procedure such as PT have arisen.

The population in the present study is a carefully selected group of patients in whom the diagnosis of CTPH with central, major vessel, obstruction was reasonably well established by inclusion criteria. By the time of their diagnosis and follow-up, pulmonary thromboendarterectomy was not yet available at our institution and, therefore, these patients were treated only with formal long-term oral anticoagulation. In recent years, however, pulmonary thromboendarterectomy has become a potential form of treatment for these patients and in fact, as mentioned in the section of methods, five out of the initial 21 selected patients were excluded from the present study because they successfully received this form of therapy. At pulmonary thromboendarterectomy, the diagnosis of CTPH was confirmed as these patients showed complete obstruction of the proximal pulmonary arteries by a well organized thrombus. Pathology confirmation of diagnosis was also established by the necropsy study in those CTPH patients who died in the hospital. Given the certainty in diagnosis and the relatively long period of follow-up, we believe that the group of patients in the present study, although limited in number by the strict selection criteria, represents a suitable population to learn about the natural (not surgically treated) history of CTPH.

Clinical characterization. Regarding the clinical characterization of the disease, our results are very similar to those previously reported.[1-4] As in these studies, clinical evidence for deep venous thrombosis and/or a clear-cut history for acute pulmonary embolism was present in only 36% and 40% of these patients respectively. Dysp-

nea was the universal symptom in our population, and in many of the patients progressive, disabling, shortness of breath was the only complaint at diagnosis. Both a low cardiac output and an increase in dead space may account for the presence of this symptom.[1,3] Effort-related chest pain (66.6%), hemoptysis (20%), and syncope or near syncope (26%) were also present. It is interesting to note that both orthopnea and paroxysmal nocturnal dyspnea were also reported by a significant proportion of patients (46% and 26% respectively) in our study. These symptoms are usually attributed to left-sided congestive heart failure, however, in the setting of CTPH they might be a reflection of severe right ventricular dysfunction as it has been shown in other forms of severe pulmonary hypertension.[19] The physical findings of our patients are those usually found in any patient with pulmonary arterial hypertension and variable degrees of right ventricular dysfunction.[1-4,16,19] The characteristic continuous murmur over the lung fields which is accentuated by full inspiration[1-3,20] was found in only three of our patients. The radiological, electrocardiographic, and echocardiography findings of cor-pulmonale (i.e. right ventricular hypertrophy) in our patients are in support of the chronicity of the disease and they also point-out the fact that unfortunately, most of CTPH patients look for medical attention late in the course of their disease.

Pulmonary hemodynamics. The hemodynamic findings are also similar to those previously described.[1-4] CTPH patients in our study had severe pulmonary hypertension and variable degrees of right ventricular dysfunction as assessed by the increase in right ventricular end-diastolic pressure and/or a decrease in cardiac index. The pathophysiologic basis for the pulmonary arterial hypertension in this setting have been previously established.[1-4,21,22] The increase in pulmonary vascular resistance in CTPH is mainly the result of the mechanical obstruction of the pulmonary circulation imposed by the unresolved pulmonary thromboembolism but other factors may also be important. Open lung biopsies performed at the time of pulmonary thromboendarterctomy in CTPH patients have shown significant structural vascular changes in the non-obstructed vascular bed of these patients. These morphologic vascular changes at the microvasculature have varied from medial hypertrophy to “plexiform” lesions. This vascular remodeling in the “open” vessels appears to be result of the pulmonary hypertension per se and it represents the morphologic basis to explain the relatively slow hemodynamic deterioration that occurs in most of the CTPH patients.[1-3,21,22] Other factors such as active hypoxic vasoconstriction do not appear to play a significant role in the genesis of pulmonary arterial hypertension in this setting; indeed, pulmonary vascular resistance was not modified by oxygen breathing in our patients. However, the role of chronic hypoxia on the remodeling of the pulmonary vasculature and in the increase of pulmonary vascular resistance in CTPH remains unknown.

Although the level of mean pulmonary artery pressure in CTPH is similar to that found in patients with primary pulmonary hypertension,[16,19,23] it is our impression that patients with CTPH tend to have lower levels of pulmonary artery diastolic pressure than primary pulmonary hypertension (PPH) patients. To emphasize this point we have compared the baseline pulmonary artery pressures of adult patients with primary pulmonary hypertension (n = 42) in our population,[16] to those of CTPH patients who have had a pulmonary thromboendarterectomy at our institution (n = 15). Even though the mean pulmonary artery pressure is the same in both groups (CTPH = 8.1 (1.45) kPa, PPH = 8.66 (2.39) kPa, p = n.s.), patients with CTPH have lower diastolic pulmonary pressure (5.06 (1.06) *vs* 6.26 (1.86) kPa, $p < 0.02$) than PPH patients. Likewise, the pulmonary pulse-pressure (i.e. systolic minus diastolic pulmonary pressures) is higher in the group of CTPH patients (8.74 (1.99) *vs* 6.66 (2.26) kPa, $p < 0.003$). In other words, in patients with CTPH the systolic component of the pulmonary artery pressure appears to be more important. This is not an unexpected finding as it has been established that changes in the systolic component of the pulmonary artery tracing are associated more with changes in the compliance characteristics of the large, elastic, pulmonary vessels whereas the diastolic component reflects more appropriately the existence or not of vascular obstruction at a microvasculature level at the end of diastole.[24,25] It is interesting to note that this type of behavior of the pulmonary artery pressure trace is similar to the experimental counterpart of central and peripheral vascular obstruction in canine models of pulmonary arterial hypertension.[26] Although speculative, this observation might be an important one. The simple analysis of the pulmonary pressure tracing could be useful for differential diagnosis as well as for prognostic purposes. Patients with primary pulmonary hypertension will always have a significant diastolic component in their mean pulmonary artery pressure whereas in CTPH patients this component is not usually as important. Moreover, if in a given CTPH patient this diastolic component is significantly increased, it may be then assumed that vascular remodeling at the pulmonary microvasculature level in the non-obstructed pulmonary vascular bed of this patient might have occurred. The existence of these hypertensive vascular changes in the open vessels may explain the deterioration which these patients experience preoperatively over time,[21] the existence of vascular steal after pulmonary thromboendarterectomy,[22] and finally they might influen-

ce the immediate postoperative hemodynamic behavior of some of these patients.[21] It has been recently shown that these lesions can resolve over time with the relief of pulmonary hypertension.[22]

Survival. Chronic thromboembolic pulmonary hypertension is a relatively rare form of chronic secondary pulmonary hypertension and it represents one of those infrequent examples in medicine in which a successful therapeutic approach for the pathologic condition became available before the precise pathogenesis and natural history of the disease could be elucidated. Accordingly, most of the information regarding survival in this disease has been extrapolated from other studies on survival in pulmonary embolism.[1-4] One of the studies more often quoted is that of Riedel et al,[27] in which 76 patients with various forms of pulmonary thromboembolic disease were followed up for one to fifteen years. According to the clinical presentation, these patients were classified into four groups: acute pulmonary embolism, sub acute pulmonary hypertension, recurrent pulmonary hypertension, and occult pulmonary hypertension. Important results and conclusions of that study were: first, that significant chronic pulmonary hypertension (PAP > 3.99 kPa) is a rare complication of acute, subacute, and even after recurrent pulmonary embolism. Second, that it is in the group of patients with occult pulmonary embolism that significant pulmonary hypertension exists from the first examination. Death from pulmonary arterial hypertension was also proportionally higher in this group. Finally, when all these four clinical groups were combined, mortality correlated with the level of pulmonary artery pressure and with the presence of right ventricular failure. In an extended part of this study, another 71 patients were added to the original series for a total of 147 patients. By doing this, it was possible to assess the cumulative survival of patients with pulmonary embolism according to the level of mean pulmonary artery pressure. From this analysis it becomes clear that patients with mean pulmonary artery pressure over 5.33 kPa, which corresponds to the level of pressure usually seen in CTPH patients, have a five-year survival probability of only 30%. Moreover, when the mean pulmonary artery pressure is more than 6.66 kPa, the chance of survival decrease to only 10%. Given the different design of our study, it is remarkable how our results fit with the above assessment of survival. Although our study was restricted to patients in whom the diagnosis of CTPH (with major vessel obstruction) was established, the patients as a group had a mean (SD) level of mean pulmonary artery pressure (6.93 (2.3) kPa) that corresponded to a five-year survival probability of less than 20% as it would have been predicted by the Riedel et, al. Study.[27]

Factors associated with survival. Results of the univariate and multivariate analysis in the present study showed that variables with physiological significance such as an increased physiological dead space and a decreased arterial oxygen content might be related with an increased risk of death. To our surprise no other functional or hemodynamic variables were associated with such a risk. We do not have a clear explanation for this finding as hemodynamic variables in particular those reflecting right ventricular dysfunction have been shown to be important in other human models of pulmonary hypertension.[16,23,28] We believe that our analysis in the present study is limited by two facts. First, by the small number of patients and the retrospective nature of the study and second, by the fact that the hemodynamic profile at entry in the CTPH patients of the present study is quite homogeneous. Given the above limitations, it is difficult to obtain any firm conclusion regarding the factors associated to survival in CTPH.

Despite of the fact that the level of PAP in CTPH patients may appear lower than that observed in adult patients with primary pulmonary hypertension[16] (6.93 (2.13) *vs* 8.66 (2.39) kPa), the survival expectancy in CTPH is worse than that in PPH *(figure 1)*. According to the multivariate analysis we performed, this difference in survival does not appear to be explained only by the different age range in both series. Although speculative, another possible explanation would be that, as discussed above, the right ventricle afterload may differ in both models of human disease and this might influence survival. In other words, right ventricular afterload is more than pulmonary artery pressure and pulmonary vascular resistance. Impedance to right ventricular output is also influenced by pulmonary vascular compliance and pulsatile flow. In particular, the efficiency of the right ventricle as a pump is significantly influenced by the compliance characteristics of the pulmonary vasculature,[26,29] and proximal arterial constriction or obstruction (as in CTPH) produces a more formidable right ventricular dynamic afterload than lung microvasculature obstruction (as in PPH) to a similar pressure elevation.[26] The present study, however, does not allow to draw any firm conclusion in this regard and the possibility of a different right ventricular afterload in these two diseases remains only speculative.

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