ORIGINAL ARTICLES

Lung Function Testing in Patients With Pulmonary Arterial Hypertension

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OBJECTIVE: The main objective was to describe the results of lung function testing in a series of 120 patients with pulmonary arterial hypertension, and the secondary objective was to compare these findings with hemodynamic variables.

PATIENTS AND METHODS: This was a descriptive study of lung function in 120 patients with stable pulmonary arterial hypertension (Evian/Venice groups 1 and 4) studied until January 2002 in the Pulmonary Hypertension and Lung Transplant Working Group attached to the Cardiology Department of the Hospital Universitario 12 de Octubre in Madrid, Spain. Data were collected retrospectively for the first 47 patients (1981 to 1995) and prospectively thereafter for the remaining 73 patients. The diagnosis was idiopathic arterial hypertension or hypertension associated with collagen disease, chronic pulmonary embolism, cardiac shunt, or toxic oil syndrome (30 cases).

RESULTS: In the group as a whole, forced vital capacity, forced expiratory volume in 1 second, and total lung capacity were normal; mean (SD) values revealed low carbon dioxide diffusing capacity (67.6% [23.2%]), and moderate hypoxemia (65.8 [15.4] mm Hg). No significant associations were observed between lung function and hemodynamic parameters. Mean age in the toxic oil syndrome group was lower (33.7 [11.4] years), and these patients had higher mean scores on the New York Heart Association scale (3.3 [0.5]) and for pulmonary vascular resistance (20.3 [8.1] kPa·L^{-1}·s).

CONCLUSIONS: Lung function was studied in a series of 120 patients with pulmonary arterial hypertension (Evian/Venice groups 1 and 4), 30 of whom had toxic oil syndrome. No significant associations were found between lung function and hemodynamic parameters.

Key words: *Lung function tests. Pulmonary hypertension: physiopathology, diagnosis.*

Exploración funcional pulmonar en pacientes con hipertensión arterial pulmonar

OBJETIVO: El objetivo principal es la descripción de los hallazgos funcionales respiratorios en una serie de 120 pacientes con hipertensión arterial pulmonar (HAP), y el objetivo secundario es su comparación con los datos hemodinámicos.

PACIENTES Y MÉTODOS: Estudio descriptivo de la función pulmonar de los 120 casos con HAP estable, de los grupos 1 y 4 de Evian/Venecia, estudiados hasta enero de 2002 en el grupo de trabajo de Hipertensión Pulmonar y Trasplante de Pulmón del Servicio de Cardiología del Hospital Universitario 12 de Octubre de Madrid. Los datos de 47 pacientes se recogieron retrospectivamente desde 1981 a 1995, y de forma prospectiva en los 73 restantes. Se incluyeron casos de hipertensión arterial idiopática y de la asociada a colagenosis, tromboembolia pulmonar crónica, *shunt* cardíaco y, en 30 casos, a síndrome de aceite tóxico (SAT).

RESULTADOS: En el conjunto del grupo la capacidad vital, el volumen espiratorio forzado en el primer segundo y la capacidad pulmonar total fueron normales; los valores medios mostraron un factor de transferencia bajo (media ± desviación estándar: 67,6 ± 23,2), e hipoxemia moderada (65,8 ± 15,4 mmHg). No se observaron asociaciones significativas entre los parámetros funcionales pulmonares y los hemodinámicos. El grupo con SAT tenía la edad más baja (33,7 ± 11,4 años), junto a los valores medios más altos en la escala de la New York Heart Association (3,3 ± 0,5) y de resistencias vasculares pulmonares (20,3 ± 8,1 kPa·l^{-1}·s).

CONCLUSIONES: En este trabajo se estudia la función pulmonar en una serie de 120 pacientes con HAP, de los grupos 1 y 4 de Evian/Venecia, entre los que se incluyó a 30 casos con SAT. No se han encontrado asociaciones significativas entre los valores funcionales respiratorios y los hemodinámicos.

Palabras clave: *Pruebas de función pulmonar. Hipertensión pulmonar. Diagnóstico de la hipertensión: fisiopatología, pulmonar.*

Introduction

Pulmonary arterial hypertension (PAH) is a common respiratory disorder with various clinical presentations.[1,2] It is primarily a complication associated with cor pulmonale and chronic respiratory insufficiency particularly in the context of chronic obstructive

pulmonary disease and less often diffuse interstitial disease, sleep apnea syndrome, and central alveolar hypoventilation. Pulmonary venous hypertension is also a common associated condition. Less common are idiopathic PAH and PAH associated with entities such as collagen disease, toxic oil syndrome (TOS),[3] human immunodeficiency virus infection, intracardiac shunt, chronic pulmonary embolism (PEc), and portal hypertension. Other less common causes are sarcoidosis, schistosomiasis, and pulmonary hemangiomatosis.

Information on lung function in the different types of PAH is scant, and no such information is available for patients with TOS. The main objective of this study was to describe the results of lung function testing in a series of 120 patients with PAH, and the secondary objective was to compare these findings with hemodynamic variables.

Patients and Methods

Lung function was studied in 120 patients with PAH whose condition was stable in the short term. Patients with lung disease associated with hypoxemia were excluded. The study population included all the cases of PAH studied until January 2002 by the Pulmonary Hypertension and Lung Transplant working group attached to the Cardiology Department of the Hospital Universitario 12 de Octubre in Madrid, Spain. Information was collected retrospectively for the first 47 patients (1981 to 1995) and prospectively thereafter for the remaining 73 patients. This was a prospective, retrospective, and descriptive study.

Lung function and hemodynamic variables were analyzed as well as the patients' age, sex, and New York Heart Association (NYHA) functional class. Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV$_1$), total lung capacity (TLC), and carbon monoxide transfer factor (TLCO) were measured using MasterLab (Jaeger, Wurzburg, Germany). The results were expressed as percentages of the respective reference values established by the European Respiratory Society.[4] PaO$_2$ and PaCO$_2$, expressed in mm Hg, were measured using an IL 1306 gas analyzer (Instrument Laboratories, Inc., Lexington, Massachusetts, USA) in a blood sample drawn from the brachial artery while the patient was breathing ambient air. The 6-minute walking test was performed on a Jaeger treadmill. Oxygen saturation was monitored by pulse oximetry (Pulsox-7, Minolta, Osaka, Japan). The following hemodynamic variables were measured at rest: mean aortic and pulmonary arterial pressure (MPAP) in mm Hg, cardiac index (in L·min^{-1}·m^{-2}), and systemic and pulmonary vascular resistance (in mm Hg·L^{-1}·min).

Lung function and hemodynamic testing was carried out before any treatment was given for PAH and during the same hospital stay. As patients were tested at different points in the course of their disease, the differences observed cannot be extrapolated to the diseases that produced them.

Statistical Analysis

In the analysis of sample size, it was noted that the number of variables was large and that many of them were of necessity not independent. The first step was to identify the independent variables that provided predictive information: a

TABLE 1
Population Studied*

Pulmonary Hypertension	Males	Females	M:F	Total
Idiopathic	15	33	1:2.2	48
Toxic oil syndrome	10	20	1:2	30
Collagen disease	3	14	1:4.7	17
Chronic pulmonary embolism	5	5	1:1	10
Left-to-right shunt	3	8	1:2.7	11
Aids	1	2	1:2	3
Appetite suppressant use	0	1	0:1	1
Total	37	83	1:2.2	120

*M:F indicates male-to-female ratio.

correlation matrix was created to identify reliable lung function variables that correlated with the hemodynamic variables (r>0.20, P<.05) by means of univariate analysis of variance in the 5 diagnostic groups. Variables were retained for the multivariate analysis when the null hypothesis (that the mean values for those variables were similar in the different diagnostic groups) was rejected. Several multivariate regression models were fitted to determine whether lung function variables could explain hemodynamic variables.

Results

Data was collected from 120 patients (37 men and 83 women). Mean age was 41.8 years (Table 1). Three patients had been diagnosed with AIDS and in 1 case the PAH was induced by an appetite suppressant drug. The remaining 116 patients were distributed into 5 main diagnostic groups using the Evian/Venice classification criteria[1,2]: a) idiopathic, no etiologic agent identified; b) TOS, fulfilling clinical and epidemiological criteria; c) various types of connective tissue disease in accordance with conventional clinical criteria; d) left-to-right cardiac shunt diagnosed by way of hemodynamic assessment and echocardiography; and e) PEc confirmed by pulmonary angiography or helical computed tomography. Shunt was a persistent ductus arteriosus in 5 cases, interventricular in 2, and interauricular in 4. The types of collagen disease were as follows: 8 patients had systemic sclerosis, and 5 of these had CREST (calcinosis, Raynaud disease, esophageal dysmotility, sclerodactyly, telangiectasia) syndrome; 4 had mixed collagen disease; 3, antiphospholipid syndrome; 1, systemic erythematous lupus; and 1, rheumatoid arthritis.

The findings for the patients allocated to the 5 diagnostic groups (n=116) and for the study population as a whole (n=120) are shown as means (SD) in Table 2.

Mean age overall was 41.8 years. The mean age of the TOS group was significantly lower than that of all the other groups except the shunt group. There were more women than men in the study population as a whole (male-to-female ratio, 1:2.2). The sexes were distributed equally in the PEc group, but women were in the majority in all the other groups, particularly in the group of patients with collagen disease (82%).

The majority of patients (75%) were classified as NYHA class III, and the mean for the group as a whole

TABLE 2
Means (SD) of the Variables Studied for the Study Population as a Whole and for the 5 Main Diagnostic Groups*

	Total	Idiopathic	TOS	Collagen Disease	Shunt	PEc
No. of patients	120	48	30	17	11	10
Age, years	41.8 (15)	44.7 (14.2)	33.7 (11.4)	46.1 (14.5)	36.3 (19.5)	50 (17)
NYHA	3 (0.5)	3 (0.5)	3.3 (0.5)	3.1 (0.3)	2.8 (0.6)	2.8 (0.6)
FVC, %	85 (15)	86.5 (16.2)	85.6 (13.9)	86.2 (12.4)	72.8 (18)	75.4 (9.9)
FEV_1, %	83.5 (15.8)	84.7 (17.6)	83.9 (14.4)	83.9 (13.7)	76.6 (16.5)	77.9 (13.6)
TLC, %	93.7 (16.7)	97 (15.2)	93.8 (17.9)	91.8 (14.6)	86.4 (23.5)	75 (5.7)
TLCO, %	67.6 (23.2)	72 (22.8)	62.8 (20)	59.2 (25.7)	85.8 (35.7)	63.9 (13.5)
PaO_2, mm Hg	65.8 (15.4)	65.4 (18.4)	72.1 (11.7)	63.6 (14.4)	56.9 (12.1)	59.8 (7.9)
$PaCO_2$, mm Hg	31.7 (4.6)	32.2 (4.3)	30.9 (4.8)	30.8 (5.3)	31 (3.5)	31.9 (6)
PCP, mm Hg	10.4 (4.5)	10.2 (4.3)	11.9 (5.4)	10.3 (13.3)	11 (7)	8.3 (1.9)
MPAo, mm Hg	91.5 (15.1)	91.2 (13.6)	90.9 (13)	92.3 (13.9)	100 (27)	80.7 (13.8)
MPAP, mm Hg	63.8 (15.3)	59.6 (13.9)	71.1 (13.5)	58.2 (10.7)	80.9 (19.9)	56 (17)
CI, $L \cdot min^{-1} \cdot m^{-2}$	2.1 (0.8)	2 (0.6)	2 (0.6)	2.4 (1.3)	3.2 (2.04)	2.1 (0.4)
SVR, $kPa \cdot L^{-1} \cdot s$	28.3 (11)	30.5 (12.4)	26.9 (6.4)	25.4 (14.1)	20	
PVR, $kPa \cdot L^{-1} \cdot s$	17 (8)	16.4 (8)	20.3 (8.1)	14.7 (7.3)	13.1 (5.9)	14.3 (5.9)

*TOS indicates toxic oil syndrome; PEc, chronic pulmonary embolism; NYHA, New York Heart Association functional class; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; TLC, total lung capacity; TLCO, carbon monoxide transfer factor; PCP, pulmonary capillary pressure; MPAo, mean pulmonary aortic pressure; MPAP, mean pulmonary artery pressure CI, cardiac index; SVR, systemic vascular resistance; and PVR, pulmonary vascular resistance.

TABLE 3
Summary of the Results of the Multivariate Analysis Performed Using a Multiple Regression Model*

Explained Variable	Explanatory Variables				Model Efficacy	
	Age, Coefficient (P)	Sex, Coefficient (P)	TLCO, Coefficient (P)	Diagnosis, Coefficient (P)	P	Adj R-Sq
SPAP	−0.04 (.10)	1.3 (.08)	0.26 (.01)	11.6 (.04)	0.039	.08
MPAP	−0.10 (.44)	1.8 (.64)	0.14 (.07)	9.2 (.03)	0.04	.13

*TLCO indicates carbon monoxide transfer factor; SPAP, systolic pulmonary arterial pressure; MPAP, mean pulmonary arterial pressure; Adj R-Sq, Adjusted R-Squared, the coefficient of determination.

was 3. The NYHA class of patients with TOS was significantly higher than that of other groups except for the patients with collagen disease. MPAP was 60.9, 65.3, and 65.5 mm Hg respectively for patients in NYHA classes, 2, 3, and 4.

In the study population as a whole, we found mild hypocapnia due to hyperventilation and moderate hypoxemia. FVC, FEV_1, and TLC were normal, and TLCO was low (67.6% of the predicted mean). The mean distance covered in the 6-minute walking test was 342.8 (103.7) meters with a desaturation of 5.1% (5.3%). While pulmonary capillary pressure, mean aortic pressure, and systemic vascular resistance were normal, MPAP values were markedly high. Cardiac index was low, and pulmonary vascular resistance high.

FVC tended to be slightly decreased in the shunt and PEc groups, and the difference was significant between the PEc and collagen disease groups. The pattern for FEV_1 was similar, but no significant differences were observed. No airway obstruction was found. The patients with shunt had the best TLCO results, possibly because this was the group with the best cardiac index. Hypoxemia was less pronounced in the TOS group, and mean $PaCO_2$ was similar in all groups. No correlation was observed in this case series between MPAP and the distance walked in 6 minutes or the degree of desaturation produced. The highest MPAP was found in the shunt group, and the second highest in the TOS group; means for both of these groups differed

significantly from the means of the other groups. The shunt group had the highest cardiac index, the mean for this group being significantly different from that of the idiopathic PAH and TOS groups. The TOS group had the highest mean pulmonary vascular resistance, and the shunt group the lowest.

In the series as a whole, no associations were found between lung function and hemodynamic parameters. Univariate analysis revealed associations only between the ventilatory parameters themselves (FVC, FEV_1, and TLC) on the one hand, and between the hemodynamic variables (mean aortic pressure and MPAP) with their respective vascular resistances and the cardiac index on the other hand. No significant associations were found for TLCO. PaO_2, $PaCO_2$, MPAP, and cardiac index were significantly associated with age. In the TOS group, however, age was not associated with those variables, but TLCO correlated with vascular resistance. In the same group, NYHA class was also significantly associated with FEV_1 and vascular resistance. An association between TLCO and PaO_2 was observed in the collagen disease group.

Data for only 82 of the 120 patients were included in the multiple regression analysis; this weakens the results and could increase random error. The regression models explained hemodynamic variability better than the mean for each included variable alone in the case of systolic pulmonary arterial pressure and MPAP. The variables that explained the variation in systolic

pulmonary arterial pressure and MPAP were TLCO and diagnostic class. In any case, the model only explained between 8% and 13% of the variance in systolic pulmonary arterial pressure and MPAP, indicating that other unstudied factors must be responsible for changes in those parameters (Table 3).

Discussion

This case series was subdivided into 5 clearly defined diagnostic groups. In addition to the patients with idiopathic PAH, there were cases of PAH caused by collagen disease, shunt, and PEc. The fifth group was more unusual, being composed of patients whose underlying disease was TOS. We have published various studies on this syndrome, which may result in death caused by PAH.[5-13]

The differences observed in sex distribution must be related to the underlying disease and introduce no additional differences in the presentation of PAH. No sex-related differences were found in the variables studied. One group of authors found significantly lower TLC in women,[14] but in our study the mean for this variable was lower in men. The most marked sex-related difference observed was in TLCO, which tended to be lower in women but not significantly so.

Although it is estimated that 6.4% of patients with idiopathic disease have familial PAH,[14] that was not so for any of the 48 patients in the idiopathic group in this case series.

Various excellent general reviews of PAH have been published,[14-16] and the pathogenesis of this disease is currently under review as a result of recent findings.[17-31] However, few large case series have been reported. The aspects most often studied have been response to therapy[22,23] and PAH in the context of sleep-disordered breathing[24] and chronic obstructive pulmonary disease.[25] These studies also make scant reference to lung function.[14,26-30]

Our lung function findings are consistent with those previously published.[3,14,27] No obstructive pattern was revealed by spirometry. FVC and TLC were normal or there was only a slight decline in FVC. A marked decline in TLCO, moderate to severe hypoxemia, and slight hypocapnia were observed. No statistically significant associations have been reported for pulmonary arterial pressure resting[28] or during exercise,[29,32] and no such associations were found in the present study either.

A decrease in TLCO has been studied as a factor that predicts the development of PAH in patients with diseases that increase risk, such as collagen disease and TOS. In a study of patients with CREST syndrome,[33] a TLCO value lower than 43% of predicted was shown to have a sensitivity of 67% for the detection of PAH. In one of our case series comprising 11 patients with TOS without clinical evidence of PAH selected because they had a TLCO lower than 50% of predicted, 3 had PAH when resting and 7 during exercise; in the group as a whole, MPAP went from 20.7 mm Hg (resting) to 35.3 mm Hg (during exercise).[9]

Although it has been reported that TLCO may be normal or only slightly diminished in patients with PEc,[28] in the present study it was also low in this group possibly because of retrograde perfusion of the capillary bed from the bronchial arteries with high flow. In a study of patients with idiopathic and thromboembolic PAH, both components of TLCO were decreased: membrane diffusing capacity and, to a lesser degree, pulmonary capillary blood volume.[29] In that study, the decrease in membrane diffusing was significantly associated with increased pulmonary vascular resistance. In another study, PEc patients treated with thromboendarterectomy presented a decrease in TLCO caused principally by reduced membrane diffusing capacity, which declined even further after surgery.[30] The decline in membrane diffusing capacity in these 2 studies may have been related to the monoclonal endothelial cell proliferation observed in idiopathic PAH.[21]

It has been reported that the distance covered by patients in the 6-minute walking test correlates highly with death caused by PAH.[32,34] What happens during exercise has been studied at maximal and submaximal intensity. The 6-minute walking test, the most common test at the submaximal level, provides similar information to tests involving maximal effort and is better tolerated by the patients.[34] The fact that the patients in our study walked on a treadmill rather than along a corridor could increase the dispersion of the results.

In our study, the shunt group had the highest pulmonary arterial pressures and the TOS group the second highest. While patients in the shunt group maintained a relatively normal cardiac index and had lower pulmonary vascular resistance values, the TOS patients had a very low cardiac index and the highest pulmonary vascular resistance levels in the study. The TOS group was the only subgroup in which we observed a significant association between TLCO and pulmonary vascular resistance levels.

The natural history of idiopathic PAH and PAH related to collagen disease, shunt, and PEc is one of progressive evolution. However, spontaneous regression occasionally occurs in cases of PAH initially considered to be idiopathic,[35] and when PAH is secondary to a specific condition it may improve or disappear when said condition disappears.

The characteristics of the TOS group distinguish it from the others analyzed. The ratio of males to females among the more than 20 000 patients on the official register of patients suffering from TOS is 1 to 1.92[7]; the ratio in our series was 1 to 2. Mean age in the TOS group was lower, and these patients scored highest on the NYHA scale. The results of conventional spirometry were normal; in an earlier study 2% of TOS patients were found to have an obstructive pattern secondary to concomitant respiratory diseases, such as asthma or bronchial hyperreactivity.[10] The decrease in TLCO is slightly more marked in patients with collagen

disease, but the PaO_2 in these patients is the highest of any of the groups. Analysis of the course of TLCO changes over time revealed a general trend towards improvement. This regressive trend was also observed in PAH, although it was impossible to quantify it with any precision.[29] In a subset of patients, however, the evolution tended towards progressive deterioration.

In conclusion, a series of patients with PAH, including a number suffering from TOS, were studied. The collection of homogeneous data facilitated a comparison between lung function and hemodynamic variables and between the different diagnostic groups. No significant associations were observed between lung function and hemodynamic parameters. Compared to the other groups, the patients with TOS (absent from other studies) had the lowest mean age and the highest NYHA class and pulmonary vascular resistance values.

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