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ORIGINAL ARTICLE

Pulmonary hemodynamics as predictors of mortality in patients awaiting lung transplantation

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Summary

Lung transplantation (LTx) is a therapeutic option for patients with end-stage lung disease. However, the mortality rate of patients on the waiting list is high. The purpose of this study was to examine the prognostic value of cardio-pulmonary hemodynamics for death in patients awaiting LTx. Retrospectively, 177 patients with advanced lung disease accepted for LTx at Sahlgrenska University Hospital from January 1990 through December 2003 were studied. Patient demographics, pulmonary function tests, gas exchange and hemodynamic variables were included in the analysis. Death while awaiting LTx was the primary endpoint for all analyses. Mean age was 49 ± 9 years. Main diagnoses were alpha 1 antitrypsin deficiency ($n = 56$), chronic obstructive pulmonary disease ($n = 61$), cystic fibrosis ($n = 14$) and interstitial lung disease ($n = 46$). Thirty patients died (17%). LTx was performed in 143 cases. By univariate analyses, forced vital capacity (FVC) % of predicted, pulmonary vascular resistance (PVR) and diagnosis were associated with risk for death. In multivariate analysis PVR (HR, 1.22; 95% CI, 1.06–1.41; $P = 0.006$) and FVC% of predicted (HR, 0.97; 95% CI, 0.94–0.99; $P = 0.01$) were independently associated with death. Patients with increased PVR and a lower FVC % of predicted awaiting LTx should be considered for a higher organ allocation priority. Assessment of pulmonary hemodynamics needs to be considered during evaluation for LTx.

Introduction

Single and bilateral lung transplantation (LTx) has become an established therapeutic procedure in end-stage pulmonary disease [1,2]. However, patients who are listed for LTx face a long waiting time. The main reason for this is the shortage of donor organs and this contributes to death in patients awaiting LTx. Mortality on the waiting list is approximately 20% in most centers [3–5]. Previous studies have shown that the outcome during the waiting time for LTx is related to the diagnosis of the underlying lung disease. Patients with interstitial lung disease (ILD) have a worse prognosis than patients with chronic obstructive pulmonary disease (COPD) and alpha 1 antitrypsin deficiency (α1ATD).The reason for this is not fully understood [4,6–9]. The shortage of organ donors with increasing waiting time and an increasing referral rate for LTx stress the importance of optimal selection and correct prioritization on the waiting list of patients for LTx. It has repeatedly been demonstrated that in subgroups of patients with lung diseases a significant increase in pulmonary artery pressures and pulmonary vascular resistance (PVR) occur which in turn may affect right heart performance and the clinical outcome

[10–12]. However, the impact of pulmonary hemodynamics as a risk factor for death during the waiting time for LTx is unclear [11–13].

The purpose of this study was to identify risk factors for death during the waiting time for LTx and especially to investigate the prognostic value of pulmonary hemodynamics and right heart function when compared with lung function tests and gas exchange. We hypothesized that high pulmonary artery pressure and increased PVR could be associated with an increased risk for death among patients awaiting LTx.

Methods

The medical records of all 233 patients with end-stage lung disease who were listed for bilateral or single LTx at Sahlgrenska University Hospital from January 1990 through December 2003 were retrospectively reviewed. Patients with idiopathic pulmonary arterial hypertension and Eisenmenger's syndrome were excluded from the study.

Data collected during the evaluation for LTx included age, sex, height, body weight, medical history, diagnosis, the results of coronary angiography, invasive hemodynamics, echocardiography, radionuclide ventriculography, dynamic spirometric tests and arterial blood gas analysis, respectively.

Right heart catheterization was performed routinely in these patients between 1990 and 2000. Since 2001, catheterization was done invasively only in patients with signs of increased right ventricular pressure. Therefore only 76% of 233 patients underwent right heart catheterization.

Only patients who had undergone an invasive right heart catheterization were included in the final analysis ($n = 177$). The patients were divided into two groups: survivors (transplanted or still waiting) and nonsurvivors. We separately compared patients with COPD/α1ATD and ILD (idiopathic pulmonary fibrosis, sarcoidosis, histiocytosis, lymphangioleiomyomatosis and others).

All pretransplant investigations were performed at Sahlgrenska University Hospital.

Follow-up was complete and outcome was determined for all the patients by the end of the study, December 31, 2003.

This study was approved by Institutional Review Board at University of Gothenburg.

Physiological measurements

Dynamic spirometric tests were done using a Bernstein spirometer (Vitalograph, Burkingham, UK) until 1994 and then on air rolling seal spirometer (Sensormedicus, Yorba Linda, CA, USA) according to standard criteria of American Thoracic Society [14]. Arterial blood gases (ABG), PaO_2 and $PaCO_2$ were obtained keeping patients in the upright position and breathing room air.

Right heart catheterization was performed at rest using the internal jugular vein approach, with a Swan-Ganz pulmonary artery catheter (Baxter Health Care Corp, Edwards Div., Santa Ana, CA, USA).

Right heart, pulmonary and pulmonary capillary wedge pressures, and cardiac output were determined, the latter by the thermodilution method. Cardiac index was derived from cardiac output divided by the body surface area. PVR was calculated from the ratio of the transpulmonary gradient (mean pulmonary pressure minus mean pulmonary capillary wedge pressure) and cardiac output.

Statistical analysis

Data obtained from chart review were stored in a database (Microsoft Office Access). Exploratory analyses and error-check calculated fields were used to screen data for entry errors. Clean data were transferred to an SPSS worksheet (SPSS version 12.0.1 for Windows, SPSS Inc., Chicago, IL, USA) for analysis. Descriptive statistics were used to describe the patient's characteristics. Continuous data are expressed as mean ± SD and 95% CI. Comparisons between groups were performed by independent samples Student's *t*-test. Potential risk factors were initially analyzed for significant association with mortality on the waiting list using the Cox proportional hazards model for continuous variables.

Risk factors with a level of significance defined as $P < 0.05$ in the univariate analysis were included in the multivariable model. Actuarial survival was determined by the Life Table method. Kaplan–Meier graphs were used in the survival analysis and the log rank test was used to test for statistical significant differences between the curves. The scaled Schoenfeld residuals and testing of time dependent covariates were used to validate the proportional hazards assumption.

Patients who underwent LTx were discontinued from the study at the time of their operation. Patients who were alive and still waiting for transplantation on the date when the study closed were also censored.

Results

Thirty patients died on the waiting list (the nonsurvivors group, $n = 30$; 17%), 143 patients underwent LTx, and 4 patients were alive and still waiting for LTx at the end of the study period (the survivors group, $n = 147$; 83%) (Table 1). The mean waiting time for patients transplanted during the study period was 413 ± 357 days and

Table 1. Outcome of patients listed for lung transplantation (LTx) between 1990 and 2003 who underwent right heart catheterization.

Diagnosis	Accepted for LTx (*n*)	Transplanted (*n*)	Mortality on the waiting list (*n*)
α1ATD	56	49	7
COPD	61	50	9
CF	14	12	2
ILD	46	32	12
Total	177	143	30

α1ATD, alpha 1 antitrypsin deficiency; COPD, chronic obstructive pulmonary disease; CF, cystic fibrosis; ILD, interstitial lung disease.

mean time to death on the waiting list was 419 ± 400 days. Patient characteristics, hemodynamics, lung function data and gas exchange values for nonsurvivors and survivors, respectively, are presented in Table 2. Mean left ventricular ejection fraction for the entire cohort of patients was 61 ± 7% and mean pulmonary capillary wedge pressure was 7 ± 5 mmHg without any statistically significant differences between survivors and nonsurvivors ($P = 0.85$, $P = 0.97$) respectively. There were no statistically significant differences between the catheterized and noncatheterized group regarding the results of lung function tests, ABG analyses, BMI and gender. In the group of nonsurvivors PVR was higher than that in the group of survivors ($P < 0.03$). FVC% of predicted was lower ($P = 0.01$) and hypercapnia tended to be more common among nonsurvivors ($P < 0.08$).

Results of the univariate analysis of risk factors for death while awaiting transplantation are shown in Table 3. The hemodynamic variables that appeared relevant in the univariate analysis were PVR, systemic vascular resistance (SVR), mixed venous oxygen saturation (SVO_2) and right ventricular ejection fraction (RVEF) during exercise. The results of the multivariate analysis are presented in Table 4. PVR and FVC% of predicted emerged as independent factors for outcome on the waiting list. When COPD/α1ATD and ILD were compared, patients with ILD had a twofold higher mortality on the waiting list (Fig. 1). In patients with ILD, pulmonary artery mean pressures (Pam) and PVR were higher than those in patients with COPD/α1ATD (27 ± 12 vs. 22 ± 6 mmHg, $P = 0.002$ respectively 4.3 ± 2.9 vs. 3.2 ± 1.5 WU, $P = 0.002$) whereas RVEF during exercise was lower in the ILD group (0.36 ± 0.1 vs. 0.42 ± 0.1, $P = 0.005$). When survivors and nonsurvivors with ILD were analyzed separately, survivors had lower PVR (3.6 ± 1.9 vs. 6.2 ± 4.3 WU, $P = 0.007$) and higher

Table 2. Patients characteristics, hemodynamics, dynamic spirometric indices and gas exchange at time of referral for transplantation.

	Nonsurvivors		Survivors		
General characteristics	Value	*n*	Value	*n*	*P*-value
Age, year	50 ± 8	30	49 ± 9	147	0.44
Sex, female; no. (%)	16 (53)	30	91 (62)	147	0.33
BMI	21 ± 4.5	30	21.3 ± 4.2	147	0.69
Hemodynamics					
Heart rate	93 ± 12	29	90 ± 14	144	0.28
Ram, mmHg	3 ± 5	30	3 ± 2	147	0.60
Pam, mmHg	25 ± 11	29	23 ± 8	147	0.24
CI, l/min/m^2	2.8 ± 0.8	30	3.0 ± 0.7	147	0.36
PVR, wood units	4.2 ± 3.3	30	3.3 ± 1.7	147	0.03
SVR, wood units	21 ± 8.4	23	19 ± 5.2	117	0.13
SVO_2 (%)	67 ± 12	20	71 ± 5	73	0.03
RVEF – at rest (%)	38 ± 11	24	40 ± 9	130	0.37
RVEF – exercise (%)	34 ± 14	16	41 ± 10	99	0.03
Dynamic spirometric tests					
FVC%, predicted	42 ± 14	30	51 ± 17	147	0.01
FEV_1%, predicted	27 ± 15	30	25 ± 14	147	0.47
Gas exchange					
P_aO_2, kPa	7.8 ± 1.7	30	8,1 ± 1.9	143	0.48
P_aCO_2, kPa	6.3 ± 1.4	30	5.9 ± 1.1	143	0.08
Waiting time, days	419 ± 400	30	413 ± 357	147	0.94

All values, except sex are mean ± SD. BMI, body mass index; Ram, right atrial mean pressure; Pam, pulmonary artery mean pressure; CI, cardiac index; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; RVEF, right ventricular ejection fraction (radionuclide ventriculogram); SVO_2, mixed venous oxygen saturation; FVC%, forced vital capacity %; $FEV_{1\%}$, forced expiratory volume %; P_aO_2, arterial oxygen partial pressure; P_aCO_2, arterial carbon dioxide partial pressure.

Table 3. Univariate analysis of possible predictors of mortality on the waiting list.

Variable	Hazard ratio	95% CI	*P*-value
FVC%, predicted	0.96	0.94–0.99	0.003
SVO_2	0.95	0.91–0.99	0.03
PVR	1.23	1.07–1.40	0.002
SVR	1.08	1.02–1.15	0.01
RVEF-exercise	0.95	0.92–0.99	0.02
Diagnosis (ILD vs. COPD/α1ATD)	2.26	1.07–4.75	0.03
Ram	0.99	0.87–1.13	0.89
Pam	1.02	0.99–1.06	0.23
CI	0.69	0.37–1.29	0.25
P_aO_2	0.96	0.79–1.18	0.71
P_aCO_2	1.23	0.92–1.64	0.16
FEV_1, predicted	1.004	0.98–1.03	0.71
Listing year (continuous variable)	1.02	0.92–1.13	0.73
Listing year ≥ 1997	1.47	0.71–3.01	0.30

For abbreviations see Table 2.

Table 4. Multivariate analysis of predictors of mortality on the waiting list.

Variable	Hazard ratio	95% CI	*P*-value
PVR (wood units)	1.22	1.06–1.41	0.006
FVC%, predicted	0.97	0.94–0.99	0.01
Diagnosis (ILD vs. COPD/α1ATD)	1.60	0.66–3.87	0.3
P_aCO_2	1.10	0.79–1.52	0.59

For abbreviations see Table 2.

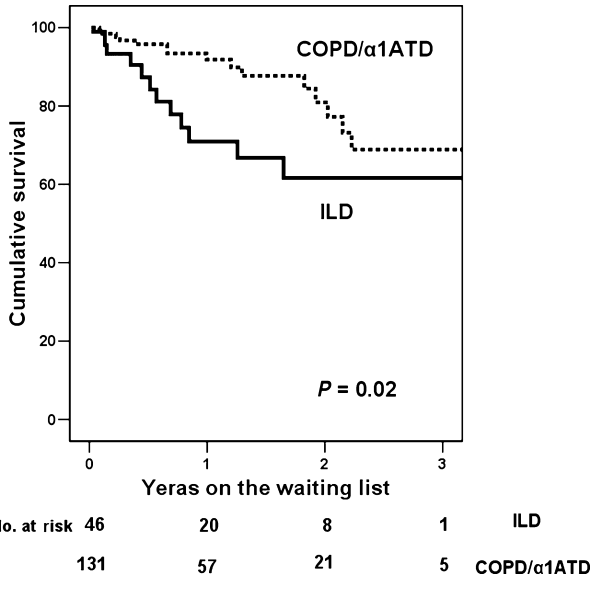

Figure 1 Differences in survival between patients with chronic obstructive pulmonary disease/alpha 1 antitrypsin deficiency and interstitial lung disease.

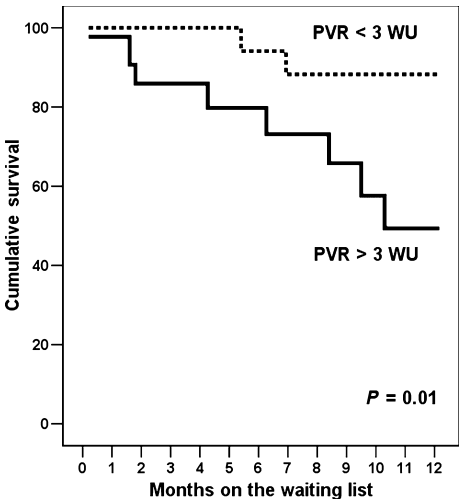

Figure 2 Probability of survival of patients with interstitial lung disease on the waiting list (determined by the Kaplan–Meier method) stratified by pulmonary vascular resistance during first year after listing for lung transplantation.

CI (3.0 ± 0.8 vs. 2.3 ± 0.6 l/min/m^2, $P = 0.01$). However lung function and gas exchange results were similar among survivors and nonsurvivors in the ILD group. The probability of survival was lower among ILD patients with PVR>3 Woods units ($P = 0.01$; Fig. 2). All deaths in the ILD group occurred within twenty months after listing (83% during the first year).

In patients with COPD/α1ATD there were no statistically significant differences in pulmonary hemodynamics between survivors and nonsurvivors (Pam 22 ± 4 vs. 22 ± 6 mmHg, $P = 0.78$; CI 3.1 ± 0.6 vs. 2.9 ± 0.6 l/min/m^2, $P = 0.22$; PVR 2.7 ± 4.3 vs. 3.3 ± 1.6 WU, $P = 0.18$) but there were significant differences in spirometric data (FVC% of predicted and FEV1% of predicted were lower in nonsurvivors ($P = 0.01$; $P < 0.0001$) respectively.

Discussion

The present study demonstrated that increased PVR is an independent predictor of pretransplant mortality in patients with end-stage lung diseases waiting for LTx. Furthermore, mortality was found to be twice as high in patients with ILD compared to COPD/α1ATD patients, which is consistent with previous studies [3,4]. Increased PVR was a risk factor for mortality in patients with ILD. However, in these patients spirometric lung function data and SaO_2 were similar among nonsurvivors and survivors. On the contrary, in patients with COPD/α1ATD, the spirometric results, but not hemodynamic data, differed significantly between survivors and nonsurvivors. Thus, although an increased PVR was found to independently

predict outcome in the whole population, this parameter seems to be more important in patients with ILD than in patients with other etiologies.

Interestingly, pulmonary artery pressure was not associated with outcome in the present study. However and importantly, mean PA pressure reflects only one aspect of pulmonary hemodynamics, while PVR is coupled to cardiac output, which in turn is dependent of cardiac function. This association is supported by the finding in the present study that a reduced right ventricular performance during exercise was found to be associated with an adverse outcome in the univariate analysis. However, assessment of RVEF was not performed in all patients and the results were therefore not included in the multivariate analysis. Almost all patients (95%) in our study had normal left ventricular ejection fraction and left heart filling pressures, which argues against left ventricular dysfunction as a contributing factor to the increased PVR. Similar findings with a stronger influence on survival by PVR compared with the pulmonary artery pressure has been reported in patients with pulmonary arterial hypertension [15,16]. In nearly 50% of the patients in the present study, PVR was pathologically increased (≥3 Wood Units), while pulmonary hypertension, defined as a mean pulmonary artery pressure of ≥25 mmHg was found only in 33% of the patients. A similar relationship has previously been reported in other studies in patients with severe lung diseases [11,17].

In previous studies PVR has not been reported separately as a predictor of pretransplant outcome in patients with lung diseases awaiting LTx. The findings in the present investigation are supported by Lettieri *et al.* [11] who recently found that in patients with severe idiopathic lung fibrosis pulmonary hypertension was associated with an adverse outcome. In their report it was also demonstrated, consistent with the results among ILD patients in the present study, that spirometric variables were not associated with outcome in this patient population. In other investigations in which pulmonary hemodynamics were reported, PVR or pulmonary artery pressures did not correlate with outcome in multivariate analysis. [12,13,18] However, those studies differ from the present regarding study population and diagnoses which makes comparison difficult. Our findings are similar to previous studies in which pulmonary artery pressures did not differ significantly between patients who died and who survived to LTx [13,18].

The mechanisms behind pulmonary hypertension and increased PVR in patients with lung diseases are not clear. Whether this is due to endothelial and vascular smooth muscle cell dysfunction, cytokine derangements, genetic factors, progressive fibrosis, hypoxemia, hypercapnia, or vascular remodeling remains uncertain [11,19–21]. Correlations between PVR and variables reflecting the severity of the pulmonary disease such as SaO_2, vital capacity and 6-min walking distance have been reported [11]. However, other reports and the present study did not find a robust relationship between dynamic spirometric indices and PVR [13]. Similarly, in a large population of patients with severe COPD investigated by right heart catheterization [22], the prevalence of severe pulmonary hypertension was 2.7%, but only 1.1% had COPD as the only identifiable cause of pulmonary hypertension. The changes in pulmonary hemodynamics were not explained by the degree of pulmonary dysfunction. The prevalence of pulmonary hypertension in patients with ILD is higher than i patients with COPD. Shorr *et al.* [23] found that approximately one quarter of more than 2000 patients with idiopathic pulmonary fibrosis who were listed for LTX in the UNOS registry had pulmonary hypertension.

Study limitations

There are several limitations in the present study. It is a retrospective review of patients who were evaluated for transplantation at a single center. A selection of patients with more advanced disease may be a limitation for an objective analysis. In addition all patients did not undergo right heart catheterization during the evaluation for LTx which may have led to selection bias. Another limitation is that data are missing from patients who has been admitted for Ltx evaluation but not accepted for the waiting list because of various reasons.

The variable 'diagnosis' in multivariate analysis should be interpreted with caution on account of a small sample size of the ILD patients.

In summary, this study demonstrated that in patients with severe lung disease, PVR was an independent predictor of death during the waiting time for LTx. Increased PVR, elevated pulmonary pressures and reduced cardiac index were most common in the ILD population. Patients with ILD had a twofold increase in mortality compared with patients with COPD/α1ATD. Furthermore, our findings indicate that pulmonary hypertension defined by increased PVR (≥3 WU) was associated with an adverse outcome, but not pulmonary hypertension defined as mPAP (≥25 mmHg at rest) underscoring the importance of not only measuring PA pressures but also cardiac output.

These results may have implications for prioritization of patients on the lung transplant waiting list regarding organ allocation. These findings also support an invasive strategy to determine pulmonary hemodynamics during the pretransplant evaluation, at least in patients with ILD. Recently, several new pharmacological interventions for treatment of pulmonary arterial hypertension have been

shown to be effective. Further studies are needed to establish whether patients with advanced lung diseases and increased PVR may benefit from treatment with these drugs as a bridging treatment until they are taken for LTx.

Authorship

NS collected the data, analyzed the data and wrote the paper. BA designed the study and analyzed the data. C-HB, GM, FN, OB-H contributed with several valuable points. BR contributed with design of the study, analysis and interpretation of data.

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