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Pulmonary hypertension before first and second lung transplantation

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Abstract

Background—Pulmonary hypertension (PH) is frequently encountered in patients with advanced lung disease before the first and second lung transplantation. We sought to determine whether there is any relationship between pulmonary hemodynamics obtained before first and second lung transplantation. We also assessed whether PH has prognostic implications in lung transplant patients going for second transplantation.

Methods—We included consecutive adult (16-yr-old or older) patients who underwent lung re-transplantation, between 1997 and 2009, and had right heart catheterization before their first and second lung transplantation.

Results—Eighteen patients were included in the study. Age at first transplantation was 50.4 (SD 10.4) yr, and bronchiolitis obliterans syndrome (BOS) in the transplanted lung was the only indication for re-transplantation. PH was observed in 39% of the patients before the first lung transplant and in 56% of the subjects before re-transplantation ($p = 0.91$). Pre-capillary PH was present in 28% ($n = 5$) and 33% ($n = 6$) of the patients before first and second lung transplantation, respectively. None of the hemodynamic variables obtained before the first transplant predicted the development of PH before re-transplantation. PH before re-transplantation did not predict survival or development of BOS after re-transplantation.

Conclusions—PH before initial lung transplantation did not predict the development of PH before the second transplantation. In our cohort, PH before second lung transplantation did not predict outcomes after re-transplantation.

Keywords

bronchiolitis obliterans; lung transplantation; mortality; outcome; pulmonary hypertension

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Authors' contributions

Adriano R. Tonelli, MD, contributed to concept/design, data collection, data analysis/interpretation, statistics, drafting the article, critical revision of the article, and approval of the article. Irina Timofte, MD, contributed to data collection, critical revision of the article, and approval of the article. Omar A. Minai, MD, and Maher Baz, MD, contributed to data analysis/interpretation, critical revision of the article, and approval of the article. Olufemi Akindipe, MD, contributed to concept/design, data collection, data analysis/interpretation, critical revision of the article, and approval of the article.

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Pulmonary hypertension (PH) is known to occur after lung transplantation particularly in patients who develop obliterative bronchiolitis, the pathological manifestation of chronic allograft rejection (1, 2). Obliterative bronchiolitis is the leading cause of mortality after the first year post-transplantation and is characterized by progressive small airway obstruction with deterioration of graft function (3–7). The term bronchiolitis obliterans syndrome (BOS) is used when the diagnosis is made on the basis of clinical rather than pathologic criteria (8, 9). BOS is defined as a drop in forced expiratory volume in one second (FEV_1) of at least 20% of the maximal baseline value after lung transplantation in the absence of other causes of declining FEV_1 (8, 10).

Lung re-transplantation is the main treatment option for advanced BOS. Previous studies in patients with BOS either used echocardiographic data or did not collect the entire hemodynamic profile during right heart catheterization (RHC) to better characterize the type of PH observed in these patients (1, 11). As such, there are not studies comparing hemodynamic measurements obtained before the first and second lung transplantation. In addition, it is unknown whether the presence of PH before the second lung transplantation has implications in terms of outcomes after re-transplantation. The purpose of the present study was to characterize the type of PH (pre- or post-capillary) (12), compare hemodynamic parameters obtained before the first and second lung transplant, and assess whether the presence of PH before re-transplant correlates with outcomes after the second lung transplantation.

Material and methods

The study was approved by the institutional review board of the University of Florida (study number: H-509-2008). Informed consent was waived as the data collection was retrospective and the research could not be carried out without this condition. We recorded information on consecutive adult (16-yr-old or older) patients who underwent lung re-transplantation and had RHC before the first and second lung transplants, between the years 1997 and 2009 ($n = 66$). Candidacy for transplantation and re-transplantation was based on criteria suggested by the International Society for Heart and Lung Transplantation (13). RHC before lung re-transplantation was ordered according to the discretion of the transplant physician. At the University of Florida, RHC is generally ordered in patients considered for second lung transplantation when the reason for re-listing is other than airway disease (dehiscence or bronchostenosis) or acute graft failure, the patient was transplanted for longer than six months and the treating physician considers that an RHC could alter management (e.g., uni vs. bilateral lung transplant, use of cardiopulmonary bypass, etc.). For the present study, we only included patients with available RHC performed at the University of Florida before the first and second RHC ($n = 18$). Calculated Lung Allocation Score was similar in patients who underwent RHC (53.6 [SD 17.7] vs. the ones who did not 53 [SD 17] $p = 0.84$).

BOS was the indication for second lung transplantation in all of our study patients. It was defined as a decrease in forced expiratory volume in one-second (FEV_1) to $<80\%$ of the patient's best baseline post-transplant value, without another identifiable source such as acute rejection, infection, airway anastomotic complications, native disease progression or recurrence (7, 8). In recipients in whom an allograft was removed during re-transplantation ($n = 7$), bronchiolitis obliterans was confirmed in all cases during histologic examination.

Data collected during the evaluation for the first and second lung transplantation included age, body surface area, indication for the procedure, flow of oxygen supplementation (L/min), pulse oximetry, FEV_1 , forced vital capacity (FVC), FEV_1/FVC ratio, and results of RHC (right atrial pressure, pulmonary artery pressure (PAP) (systolic, diastolic, and mean), pulmonary artery occlusion pressure (PAOP), and cardiac output). We calculated

transpulmonary gradient (TPG) (mean PAP–PAOP) in mmHg and pulmonary vascular resistance (PVR) (TPG/cardiac output) in Wood Units. We also determined the time from first to second lung transplants and survival after the second transplantation. Date of death of the study participants was ascertained by reviewing patient's records or by querying the U.S. Social Security Death Index. No patient was lost from follow-up.

Patients were evaluated for lung transplantation in their chronic stable state. Before re-transplantation, two patients were mechanically ventilated through a tracheostomy but were able to perform rehabilitation. Patients were not denied re-transplantation based on pulmonary hemodynamic abnormalities. Spirometry was performed following recommendations of the American Thoracic Society/European Respiratory Society task force, using appropriate spirometric reference values (14, 15). RHC was performed under mild sedation and local anesthesia using a 7F balloon-tipped pulmonary arterial catheter. All hemodynamic measurements were obtained at end-expiration. Patients on oxygen were continued on their home flow rate. Patients with decrease in pulse oximetry saturation <90% had their oxygen flow rate increased to achieve a value of 90%. Pre-capillary PH was defined as mean PAP ≥25 mmHg in association with PAOP ≥15 mmHg and a PVR ≥3 Wood Units. Post-capillary PH was defined as mean PAP ≥25 mmHg in association with PAOP >15 mmHg and PVR <3 Wood Units (12).

Statistical analysis

Continuous variables were expressed as mean and standard deviation when normally distributed. Two-group comparison was performed by Student's *t*-test or Mann–Whitney *U*-test. Paired-samples *T* test and Wilcoxon signed ranks test were used to compare continuous variables from the same patient at two time points. Comparisons between categorical data were performed by McNemar test or Fisher's exact test, when applicable. Mean PAP was dichotomized using the established cut off to define PH (mean PAP ≥25 mmHg) (4).

Time from first to second lung transplantation and survival after second transplantation were assessed by the Kaplan–Meier method. Time 0 was the date at the time of each transplant. The end of follow-up was September 7, 2009 or the time of the recipient's death. Survival analyses after re-transplantation were adjusted for age, gender, need for mechanical ventilation, and time between initial and re-transplantation, using Cox proportional hazards regression analysis (16, 17). All of the *p* values reported are two-tailed. A *p* value of <0.05 was considered significant. The statistical analyses were performed using the statistical package SPSS, version 17 (SPSS Inc., Chicago, IL, USA).

Results

We included 18 patients (12 men [67%] and 6 women [33%]), who underwent a second lung transplantation at the University of Florida and had a routine RHC performed before the first and second transplants. Age at first and second transplantation was 50.4 (SD 10.4) and 54.6 (SD 10.8) yr, respectively. Indications for the first lung transplantation included: idiopathic pulmonary fibrosis (44%, *n* = 8), COPD (39%, *n* = 7), alpha-1 antitrypsin deficiency (11%, *n* = 2), and sarcoidosis (6%, *n* = 1). BOS (stage 2 or above) was the only indication for the second lung transplantation. For the first lung transplant, patients received a single lung in 78% (*n* = 14, left lung in 64%, and right lung in 36%) and bilateral lung transplant in 22% (*n* = 4) of the cases, respectively. All patients received a single lung for their second transplant (left lung in 50% and right lung in 50%). In all but three cases, one of the initially transplanted allografts was retained after the second transplantation.

Comparison between RHCs performed before first and second lung transplantation

The time between RHC and transplantation was 9.2 (SD 8.7) months for the first transplant and 4.4 (SD 5.1) months for the second transplant. Hemodynamic parameters measured during these two RHCs are compared in Table 1. There was no difference in mean PAP between RHCs performed before the first and second lung transplants (24.7 [SD 6] mmHg vs. 25 [SD 6] mmHg; $p = 0.87$). PH was observed in 39% of the patients before the first lung transplant and in 56% of the subjects before the second one ($p = 0.91$) (Table 2). Pre-capillary PH was present in 28% ($n = 5$) and 33% ($n = 6$) of the patients before first and second lung transplants, respectively ($p = 0.65$). Post-capillary PH was present in 11% ($n = 2$) of patients before the initial and in 22% ($n = 4$) patients after re-transplantation ($p = 0.5$). Mean PAP before second lung transplantation did not significantly vary in the RHC of patients either performed before (28.3 (6) mmHg) or after (24.1 (5) mmHg, $p = 0.1$) the implementation of LAS score in May of 2005 (18).

We used Bland–Altman analysis to compare the differences between the RHC measurements obtained before the first and second lung transplant (Fig. 1). Comparison of mean PAP showed a narrow bias (-0.3 mmHg) with a wide limit of agreement (-16.8 mmHg and $+16.1$ mmHg). Twenty-eight percent of the patients had no PH in both RHCs performed before the first and second lung transplant. Similarly, 22.2% of the subjects had PH during both RHCs. Fifty percent of the patients had discordant results in relation to the presence of absence of PH between both hemodynamic studies (Table 2).

Eleven patients (61%) had a difference of ≤ 5 mmHg in mean PAP between both RHCs (Fig. 2). Of this subgroup, five patients experienced a decrease and six subjects had an increase in mean PAP. Nine patients (50%) had a change in PVR of ≤ 1.5 Wood Units between both RHCs (three subjects had a decrease and six individuals an increase in PVR). The TPG varied more than 5 mmHg between both RHCs in nine patients (five subjects had a decrease and four individuals an increase).

Time between spirometry and RHC was 3.2 (± 5.1) months before first transplant evaluation and 0.4 (± 1) months before the second transplant evaluation. No correlation was observed between spirometry parameters and mean PAP during first or second lung transplant evaluation (data not shown).

Outcomes after transplantation and re-transplantation related to PH

The median time between first and second lung transplantation was 31 months (95% CI 24–38). The median survival after the second lung transplant was 12 months (95% CI 3–21). At one yr, the survival was 52% (SE 13%). Main causes of death were infections ($n = 5$), BOS ($n = 4$), and hemoptysis ($n = 2$). The presence of PH (mean PAP ≥ 25 mmHg) before the second lung transplant, either alone or adjusted for age and gender, time between the first and second transplant, and use of mechanical ventilation did not predict survival after re-transplantation (HR: 1.9, 95% CI: 0.54–6.5, $p = 0.32$). Similarly, mean PAP, PVR, TPG, and presence of pre-capillary or post-capillary PH were not predictors of survival after the second lung transplant ($p = 0.56$, 0.43, and 0.17, respectively). The presence of PH before lung re-transplantation did not predict BOS after lung re-transplantation ($p = 0.99$).

Discussion

Our study showed that PH is common in patients with BOS undergoing a second transplantation and may be pre- or post-capillary in nature. We found that PH before the first transplant did not predict the development of PH before the second transplant. The presence of PH before second lung transplant was not associated with increased mortality after this intervention.

Several studies have shown that patients with various forms of advanced lung diseases, being evaluated for lung transplantation, have a very high prevalence of PH (19, 20). Few have reported on the prevalence and characteristics of pulmonary hemodynamic abnormalities in patients with advanced BOS (1,11). BOS is a form of chronic lung-allograft rejection characterized by peri-airway inflammation that leads to luminal fibrosis in the form of obliterative bronchiolitis (8). Bronchiolitis obliterans is frequently associated with pulmonary arteriopathy and venopathy (1), characteristics that can potentially explain the higher prevalence of PH reported in this group of patients (1, 11).

In the present study, the prevalence of PH (predominantly of mild degree) by RHC in patients with BOS was 56%. Of patients with PH, 60% had pre-capillary and 40% post-capillary PH. Saggar et al. (1) and Nathan et al. (11) reported a PH prevalence in BOS of 72% and 32.5%, respectively. Saggar et al. (1) evaluated the prevalence of PH measured by RHC or echocardiography (right ventricular systolic pressure ≥ 45 mmHg) in post-lung transplant patients with histologic obliterative bronchiolitis. Nathan et al. (11) studied lung transplant recipients (n = 80) with BOS re-listed for transplantation within the United Network for Organ Sharing (UNOS). Of the patients with PH diagnosed by RHC, 21.5% and 42.3% had pre-and post-capillary PH, respectively (11). These authors (11) were unable to find an association between the presence of PH before the second lung transplant and to the type of primary lung disease, transplantation of single or bilateral lungs, results of spirometry, or oxygen requirements.

Possible explanations for the development of PH in BOS include (i) loss of lung tissue and associated pulmonary vascular bed (11, 21), (ii) associated vasculopathy of the allograft as a results of immune-mediated endothelial inflammation with fibrointimal narrowing of arterioles and venules (1, 11, 21, 22), (iii) associated conditions such as diastolic dysfunction or pulmonary embolism (11), (iv) upregulation of cytokines involved in the pathogenesis of PH such as transforming growth factor- β (23, 24), platelet-derived growth factor (25) and endothelin-1 (26–28), and less likely (v) uncorrected chronic hypoxemia.

Interestingly, the presence of PH before the first lung transplant did not predict the presence of PH before the second intervention. Some patients developed a similar degree of mean PAP before the first and second lung transplants, while others had marked differences between both RHCs. Although PH was present in more than half of the patients evaluated for lung re-transplantation, its presence was not associated with reduced survival after this intervention. However, we cannot elaborate on whether the presence of PH could potentially predict mortality in patients who did not receive lung transplantation. Similarly, Nathan et al. (11) were unable to demonstrate a significant impact of PH on outcomes in patients with BOS. Thus, at this point in time, it is unclear whether performing RHC and initiating PH-specific therapies would be beneficial in this group of patients. However, RHC permits the discrimination between pre- and post-capillary PH, information that can help guide appropriate treatment.

Survival after lung re-transplantation varies according to the study from 45% to 78% at one yr (16, 17, 29–32). Survival is lower in re-transplanted patients, compared to patients receiving their first allograft, mainly due to a higher prevalence of medical comorbidities (17). In our study, the survival at one yr was 51.6%, with a median survival of 12 months. PH did not predict survival after the second transplant, even after adjusting for different factors such as gender, need for mechanical ventilation, and time between first and second lung transplant (16, 17). As the majority of patients were re-transplanted after 2001 (n = 15), we did not adjust for year of transplant in our survival model (17). PH before the second lung transplant was not associated with the development of BOS after lung re-transplantation. In our cohort, only one patient developed primary graft dysfunction after re-

transplantation; therefore, no analysis was performed to evaluate whether PH was associated with the development of this complication (33–35).

The present study has a number of limitations. Firstly, we included a relatively small number of patients who underwent lung re-transplantation for BOS. Secondly, the study was retrospective and several months elapsed between RHC and first lung transplantation, thus pulmonary hemodynamics may have worsened while on the waiting list. Lastly, it is unknown whether patients who had PH prior to the first transplant normalized their pulmonary pressures at some point after the first transplantation as no routine RHC was performed to confirm this. Prior investigations do suggest that PAP tends to normalize after unilateral or bilateral transplant (36–40). In our study, of the 11 subjects who did not have PH in the evaluation before initial transplantation, 6 (54%) developed PH before the second transplant. In spite of these limitations, our study adds novel and important information to the field as it captured and compared the entire hemodynamic profile before initial and subsequent lung transplantation.

Conclusions

PH before initial lung transplantation does not predict the development of PH before the second lung transplant. In patients who develop PH after lung transplantation, both pre- and post-capillary forms can be observed. In our cohort, PH before second lung transplantation did not predict outcomes after re-transplantation.

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Fig. 1.

Comparison of right heart catheterization measurements before first and second transplant using Bland–Altman analysis. The mean difference between mean pulmonary artery pressure (mean PAP) between RCH before first and second lung transplant was -0.3 mmHg and the 95% limit of agreement was -16.8 mmHg and $+16.1$ mmHg. The mean difference in pulmonary vascular resistance (PVR) was 0.6 Wood Units with 95% limit of agreement of -3.2 and 4.4 Wood Units. The mean difference in trans-pulmonary gradient (TPG) was 1.1 mmHg with 95% LOA of -13.6 and 15.6 mmHg. The mean difference in pulmonary artery occlusion pressure (PAOP) was -1.4 mmHg with 95% LOA of -13.3 and 10.5 mmHg. (A) Hemodynamic measurements before first lung transplantation. (B) Hemodynamic measurements before re-transplantation.

Fig. 2.

Plot comparing mean pulmonary artery pressure (PAP) measurements before first and second lung transplant. (A) Hemodynamic measurements before first lung transplantation. (B) Hemodynamic measurements before second transplantation. The overall mean PAP ($n = 18$) was 24.7 (6) mmHg and 25 (6) mmHg before first and second lung transplantation, respectively ($p = 0.86$).

Table 1

Hemodynamic and spirometric testing before first and second lung transplants

	RHC before first transplant (mean [SD] or %)	RHC before second transplant (mean [SD] or %)	P
Systolic ABP (mmHg)	133 (21)	146 (17)	0.17
Diastolic ABP (mmHg)	79 (6)	89 (11)	0.18
Heart rate (bpm)	83 (15)	81 (15)	0.55
RA pressure (mmHg)	7.7 (4)	7.5 (4)	0.86
Systolic PAP (mmHg)	37.1 (10)	38 (8)	0.69
Diastolic PAP (mmHg)	17.3 (5)	19 (6)	0.40
Mean PAP (mmHg)	24.7 (6)	25 (6)	0.87
PH (%) ^a	38.9%	55.6%	0.51
PAOP (mmHg)	11.7 (4)	13 (4)	0.35
PAOP (%) 15 mmHg	22.2%	16.7%	1
CO (L/min)	4.6 (1)	5.4 (2)	0.11
CI (L/min)	2.4 (0.5)	2.8 (0.8)	0.11
PVR (Wood units)	3 (1.7)	2.4 (1)	0.2
PVR 3 Wood units (%)	50%	17%	0.11
TPG (mmHg)	12.9 (6)	11.9 (4)	0.55
SpO ₂ (%)	97 (3)	96 (4)	0.12
O ₂ flow (L/m)	2.8 (3)	1.9 (1)	0.38
FEV ₁ (% of predicted)	30.8 (19)	32.7 (17)	0.59
FVC (% of predicted)	42.5 (11)	40.8 (11.7)	0.62
FEV ₁ /FVC	56 (30)	55.9 (19)	0.98

ABP, arterial blood pressure; bpm, beats per minute; CI, cardiac index; CO, cardiac output; PAOP, pulmonary artery occlusion pressure; PAP, pulmonary artery pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RA, right atrial; SpO₂, pulse oxygen saturation; TPG, transpulmonary gradient; FVC, forced vital capacity; RHC, right heart catheterization; FEV₁, forced expiratory volume in one second.

^aPH is defined as mean PAP 25 mmHg.

Table 2

PH before first and second lung transplants

		<u>PH before second lung transplant</u>	
		No	Yes
PH before first transplant	No	5 (27.8%)	6 (33.3%)
	Yes	3 (16.7%)	4 (22.2%)

PH, pulmonary hypertension.