Bronchoscopic Interventions as a Management of Airway Complications After Lung Transplant Including Assessment of Risk Factors With Special Consideration for Pretransplant Pulmonary Hypertension

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ABSTRACT

Background. Lung transplant (LTx) is a procedure associated with risk of complications related to airway stenosis that can be treated with bronchoscopic interventions (BIs). The aim of the study was to assess the frequency and risk factors associated with increased need of bronchial interventions in the post-transplant period.

Methods. The retrospective study reviewed cases of 165 patients (63 women) who underwent LTx from April 2013 to June 2019. For dichotomous discrete variables (occurrence or lack of intervention) multivariate logistic regression analysis was performed to assess the aforementioned risk factors.

Results. BIs were required among 38.55% of lung recipients (n = 65). The number of interventions/patient/y decreases between years 1 and 2 ($P < .001$), 2 and 3 ($P = .013$), and 3 and 4 ($P < .001$); after the fourth year post LTx the differences are not statistically significant. Each 1 mm Hg above 25 mm Hg of mean pulmonary arterial pressure causes statistically significant elevation in the number of interventions by 0.7% in the first year after the procedure. The number of BIs per patient among lung recipients who received a transplant because of idiopathic pulmonary arterial hypertension was statistically significantly higher compared with patients with another underlying lung disease.

Conclusions. Airway complications developed in the post-transplant period caused a significant number of patients to be in need of BI, especially balloon bronchoplasty. The highest number of interventions occurred within the first year after LTx, and BI decreases over time. Mean pulmonary arterial pressure measured during qualification may have the ability to predict whether the patient would require BI after LTx.

LUNG transplant (LTx) is often the only proper treatment for patients with end-stage lung diseases. It is associated with risk of certain complications: airway, vascular, pleural, and those associated with the surgical wound. Some of the most common are complications in the respiratory tract. Although numerous improvements made in past decades led to a decrease in overall number of airway complications (ACs) when compared with the early era of lung transplantation, they still remain a source not only of morbidity and mortality, but they are also associated with significant functional impairment, poor quality of life, and

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increased number of hospitalizations, limiting the development of lung transplantation. The associated mortality rate according to literature varies from 2% to 4%, and the incidence of ACs varies from 1.6% to 32% [1–5]. When it comes to patients with idiopathic pulmonary arterial hypertension, such a procedure is associated with higher perioperative risk and the highest mortality rate of 23% in the first 3 postoperative months (compared with lung recipients with chronic obstructive pulmonary disease [COPD] or cystic fibrosis [CF] who have the lowest unadjusted mortality [9%]) [6]. Factors considered to cause an increased risk of such complications are duration of cold ischemia time, mechanical ventilation in both the donor and recipient, use of steroids and immunosuppressive drugs, length of the donor bronchi, surgical technique, presence of microbial agents in the recipient and donor bronchus before surgery, and postoperative infections [7–13]. There is no universally accepted system for classifying respiratory complications after LTx. Four qualification systems have been published in recent years, although they are not commonly used [7–10].

ACs can be managed with bronchoscopic interventions (BIs), which includes argon plasma coagulation, balloon dilation, stenting, laser therapy, and cryotherapy [14,15]. The frequency of these interventions correlates with the frequency of significant complications in the airways after transplant and can be used as the indicator of ACs [12]. The aim of the study was to examine the impact of individual factors on the frequency of interventions.

MATERIALS AND METHODS

The study design was single-center retrospective cohort research. We reviewed cases of 165 patients (63 women [38.18%]) who underwent LTx from April 2013 to June 2019 in Silesian Center for Heart Diseases (Zabrze, Poland). Median age at referral for LTx was 41 years. Heart-lung transplant and retransplant recipients were excluded from the study. The number of procedures of double lung transplant (DLT) was 106 (63.1%). The most common diagnoses were as follows: COPD (n = 45); CF (n = 43); primary pulmonary hypertension (n = 21); interstitial lung disease (ILD) (n = 50), and other (n = 6). Patients were qualified with following ILDs: idiopathic pulmonary fibrosis, sarcoidosis, histiocytosis, hypersensitivity pneumonitis, and lymphangioleiomyomatosis.

The following diseases were included as other: Osler-Weber-Rendu syndrome, Williams- Campbell syndrome, bronchiectasis, and pulmonary embolism. The number of patients with at least 3-, 6-, and 12-month survival was as follows: 143 (86.67%), 136 (82.43%), and 118 (71.52%) patients, respectively.

An additional objective was to assess the impact of pulmonary hypertension (PH) on AC. For that reason we reviewed cases of 66 patients with right heart catheterization data. The study group consisted of 26 women (39.39%) and 40 men (60.61%). Median age at referral for LTx was 51.5 years. PH was defined as mean pulmonary arterial pressure (mPAP) $\geq$ 25 mm Hg at rest, measured during right heart catheterization.

Airway Complications

Despite the vastness of the term “airway complication,” this article describes interventions required in case of any airway stenosis (at the bronchial anastomosis or lower, eg, bronchus intermedius), granulation, or presence of necrotic tissue. BIs were as follows: balloon bronchoplasty, stent placement, argon plasma coagulation, laser therapy, or cryotherapy. None of the studied patients presented with partial or total anastomotic dehiscence; therefore, such complication is not described in this study.

Statistical Analysis

All statistical analyses were performed with SPSS 25.0 (IBM, Armonk, NY, United States) and R 3.5.3 (The R Foundation for Statistical Computing, Vienna, Austria). The P levels less than .05 were deemed statistically significant. For analyses involving number of BI tests adequate for Poisson distribution were used since our data consisted of counts in a given period of time. Specifically, univariate and multivariate Poisson regression was used as well as Poisson test. Interaction effect of variables in multivariate Poisson regression was assessed with partial response plot. For dichotomous discrete variables (occurrence or lack of intervention) multivariate logistic regression analysis was performed. For further analysis associated with the impact of PH on a studied issue univariate Poisson regression analyses Holm’s correction was applied to preserve overall α level equal to 0.05.

RESULTS

BIs were required among 38.55% of lung recipients (n = 65). The overall number of interventions performed in our study group, breaks down as follows: 717 balloon dilations, 306 argon plasma coagulations, 165 laser therapies, 165 cryotherapies, and 71 stent placements. Taking into account the underlying disease, the number of BIs were 359 for COPD (7.98 per patient), 235 for CF (5.47 per patient), 255 for primary pulmonary hypertension with pulmonary veno-occlusive disease (12.14 per patient), 254 for ILDs (5.08 per patient), and 132 for other (22 per patient).

The correlation between the number of interventions/patient/y (IPY) and time after LTx is presented on the Fig 1. The number of IPY decreases with time, and the differences between the number of IPY in the first and following years after LTx are statistically significant ($P < .001$). What is more, the number of IPY also decreases between years 1 and 2 ($P < .001$), 2 and 3 ($P = .013$), and 3 and 4 ($P < .001$), and after the fourth year post LTx the differences are not statistically significant.

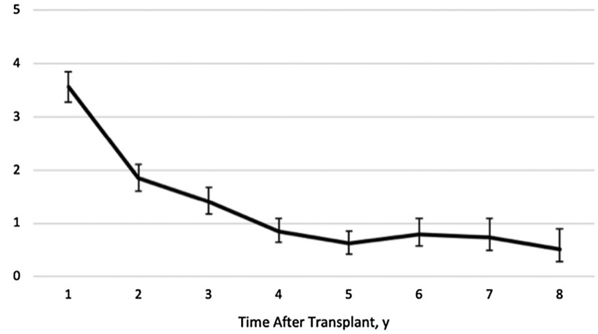

Fig 1. Interventions per patient in time after transplant.

Table 1. Multivariate Logistic Regression Analysis With Consideration of Bronchoscopic Interventions

Parameter	Parameter Assessment	SE	χ^2	*P* Value	OR	95% CI Lower	95% CI Upper
Age, y	0.022	0.035	0.404	.525	1.023	0.955	1.095
Sex, female	0.184	0.647	0.081	.776	1.202	0.338	4.276
BMI	−0.275	0.132	4.332	.037	0.760	0.587	0.984
Diagnosis							
CF	0.471	1.024	0.738	.691			
COPD	0.903	1.056	0.212	.645	1.602	0.215	11,930
Other	−1.340	0.957	0.732	.392	2.467	0.312	19,530
Diabetes	0.001	0.001	1.962	.161	0.262	0.040	1.707
Time on waiting list > 365 d	0.409	0.193	0.793	.373	1.001	0.999	1.003
CIT			4.496	.034	1.505	1.031	2.195

Abbreviations: BMI, body mass index; CF, cystic fibrosis; CIT, cold ischemia time; COPD, chronic obstructive pulmonary disease; OR, odds ratio; SE, standard error.

Univariate Poisson regression was used to find any differences between the number of interventions in the first year after LTx before 2018 and after 2018 when the change in surgical technique of bronchial anastomosis has been implemented. The decrease in overall number of BIs after 2018 can be observed, although the result is not statistically significant ($P = .06$). In multivariate logistic regression analysis, the statistical significance in Table 1 relates to Wald's statistics determining the need for performing an intervention. Statistically significant results encompassed cold ischemia time and body mass index (BMI).

An increase of BMI by each point reduces the chance of intervention by 31.6% (1316 times). Nagelkerke's R-square model was used to confirm that multivariate logistic regression analysis satisfactorily predicts the probability of having to perform interventions ($P = .246$).

If the procedure was performed before 2018, the probability of performing an intervention increased 3.6 times. Compared with DLT, single lung transplant (SLT) is associated with a 4.2-fold (95% CI, 5.42-3.32; $P < .001$) reduced chance of intervention. A statistically significant result relates to the type of operation performed. Patients after DLT have 2.2759 times more interventions than patients after SLT. If we take into account the number of anastomoses (SLT, 1; DLT, 2), we do not observe any differences between these 2 groups.

Mean pulmonary arterial pressure in aforementioned group was 33.92 mm Hg. The number of patients with PH was 38 (57.57%). Regardless of the underlying disease, the average mPAP in PH group was 45.43 mm Hg, with consideration of a given diagnosis, successively: IPAH 59.81 mm Hg (n = 16; 100%), COPD 29.56 mm Hg (n = 9; 30%), CF 27 mm Hg (n = 1; 50%), ILD 35.14 mm Hg (n = 7; 50%), and other 29 mm Hg (in bronchiectasis) (n = 1; 25%).

In our study group BIs were performed in 43.24% of recipients with PH (n = 16), while in the non-PH group, 44.83% (n = 13) of patients required an intervention.

The number of interventions per patient in the first year after LTx among PH group was as follows: IPAH 18.5, COPD 8.17, and ILD 12.66. The number of interventions per patient among lung recipients who received transplants because of IPAH was statistically significantly higher in comparison with patients with another underlying lung disease ($P < .05$).

The data from Poisson regression analysis are presented in Fig 2. In the first year after LTx, patients with PH had statistically significant higher incidence of BI than recipients without PH ($P < .05$). Moreover, in our study group there were no BIs observed after the first post-transplant year in patients without PH.

Mean pulmonary arterial pressure obtained during qualification may have the ability to predict whether the patient would require BI after LTx. Each 1 mm Hg above 25 mm Hg of mPAP causes statistically significant elevation in the number of interventions by 0.7% in the first year after the procedure.

Moreover, the following risk increases 2.3% for every 1 mm Hg above 25 mm Hg of mPAP in the second year after the procedure. Taking into consideration Holm's method and verifying whether these results are statistically significant, we obtain confirmation that in the first and second year after transplant the results remain statistically significant, although in every next year they do not cause a significant change in terms of incidence of the interventions. Entire analysis pertaining this issue is demonstrated in Fig 3.

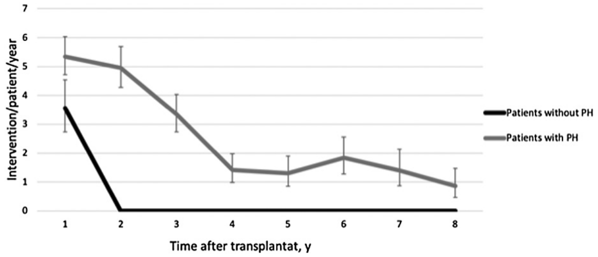

Fig 2. Interventions per patient in time after lung transplant among patients with PH and those without. PH, pulmonary hypertension.

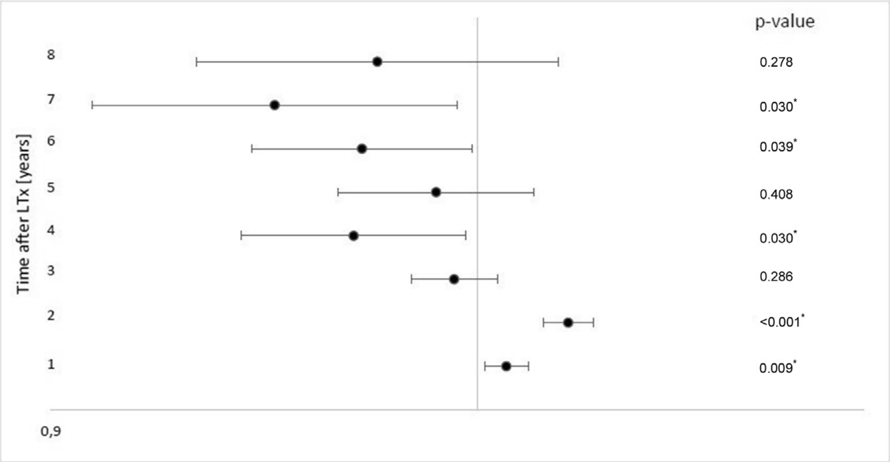

Fig 3. Univariate Poisson regression analysis (depicted as Forest plot analysis) presenting the influence of pulmonary hypertension on bronchoscopic intervention in time. LTx, lung transplant. Holm's method results in only first and second year remaining statistically significant. *$P < .05$.

DISCUSSION

Airway stenosis was noted to be the most common AC in our study. Because of that, 38.55% of recipients required BI. Available literature provides data that such complications occur among 1.6% to 32% [1–4]. The study by Herrera et al reports that in their facility the incidence of AC pertains to 23.8% of all anastomoses. Their work also emphasizes the role played by fungal infections [16]. Olland et al reported the incidence of AC at approximately 20%. Their study suggests that the change of the surgical technique pertaining special bronchial trimming as well as using absorbable sutures [3]. Our study reports significant drop of ACs requiring the BI after the year 2018, since when our surgeons changed the way they perform bronchial anastomoses. Unabsorbable sutures were replaced by absorbable ones, which are sewn continuously in the membranous part and single ones are put in the cartilage part of the bronchus. Discrete narrowing of the bronchial anastomoses were present in 4.9% of patients at 1 month and in 2.4% at 6 months after LTx, as reported by Weder et al [17]. Their study also mentions the impact of fungal infection on the healing process. This study assesses that number of BIs is the most frequent during the first year. This finding is consistent with study published by Santacruz et al, which claims that ACs occur most often between 2 and 9 months after the surgical period [2]. Our study assessed that the number of interventions required by patients decreases over time. Despite that, the study published by Mazzetta et al assessed that patients who experienced central airway stenosis in the early post-transplant period will present persistent obstructive ventilatory pattern despite endoscopic treatment, and they will experience more frequent and longer hospitalizations [18]. For these reasons, effort must be undertaken to prevent AC requiring BI.

To our knowledge, the impact of PH (both primary and secondary) on the risk of developing ACs has not been frequently evaluated; the only study that has taken into consideration the impact of PH was the study by Hyanga et al, where in multivariate analysis the impact of PH on AC remained statistically insignificant [19]. A strength of our study is the relatively high number of patients with IPAH and patients with secondary hypertension. In the current study, we have shown not only that PH predisposes to the greater risk of occurrence of AC but also the effect of higher mPAP on the increased risk of complications. What is more, it is statistically significant that patients with IPAH need more BI than patients with other underlying diseases.

CONCLUSIONS

BIs as a treatment of airway stenoses after LTx remain quite frequent. The most commonly used intervention seems to be balloon bronchoplasty. The number of BIs decreases over time. Improvement of surgical technique is associated with lesser need for BI. Cold ischemia time and BMI impact whether the patient will require the intervention. Authors are aware of study's limitation, and further research is required on a larger study group.

Pulmonary hypertension evaluated at qualification for LTx may anticipate later ACs. The higher mPAP is above 25 mm Hg, the greater chances for future AC. Patients with IPAH would require more BIs per patient, provided they will need BI. We have to take this potential risk into account and reduce any other possible risk factors that may contribute to the development of AC.

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