Patients Treated for Central Airway Stenosis After Lung Transplantation Have Persistent Airflow Limitation

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Data Collection B
Statistical Analysis C
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Background: Although central airway stenosis (CAS) is a common complication after lung transplantation, its consequences have been poorly evaluated. The objective of our study was to evaluate the impact of CAS on lung function after lung transplantation.

Material/Methods: All lung transplant recipients from June 2009 to August 2014 in a single center (Strasbourg, France) were retrospectively reviewed.

Results: A total of 191 lung transplantations were performed: 175 bilateral, 15 single, and 1 heart-lung transplantation. Of the 161 bilateral lung-transplanted patients who survived >3 months, 22 (13.6%) developed CAS requiring endobronchial treatment. All these patients were treated by endoscopic balloon dilatation, and 9 additionally needed endobronchial stents. Respiratory function tests demonstrated persistent obstructive ventilatory pattern despite endoscopic treatment in recipients with CAS compared to those without CAS at 6, 12, and 18 months post-transplant. At 18 months, CAS patients had significantly lower post-transplant FEV1 (1.96±0.60 L versus 2.57±0.76 L, p=0.001) and FEV1/FVC (61±14% versus 81±13%, p<0.001). The percentage of patients hospitalized for respiratory infections and number of hospital days were significantly increased in recipients with CAS (20 [91%] versus 92 [66%] p=0.036, and 144±110 days versus 103±83 days p=0.042, respectively). Survival in transplant recipients did not significantly differ between those with CAS and those without.

Conclusions: CAS after lung transplantation was not associated with worse survival, but it did have a significant and persistent effect on lung function, and was associated with increased rate of respiratory infection.

MeSH Keywords: Airway Remodeling • Bronchoscopy • Lung Transplantation

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Background

Bronchial complications were a real conundrum in the pioneering experience of lung transplantation in the 1960s. The primary bronchial complications were necrosis and dehiscence [1]. One possible explanation for the development of these complications is the fact that the lung is the only organ where the arterial systemic blood supply is not routinely restored during transplantation; although surgical replacement of the arterial system has been tried in the past, it failed to produce clinical improvement [2,3]. The body's natural reestablishment of the bronchial arterial circulation after lung transplantation can take up to 4 weeks. During that interval, the retrograde blood flow from the pulmonary circulation via collaterals maintains the viability of the donor bronchus [4].

Several studies showed important variations in the incidence of central airway complications after lung transplant, from 1.6% to 32%, with an associated mortality rate of 2% to 4% [5,6]. A recent analysis by our group found an incidence of central airway complications approaching 20% in a large group of lung transplant recipients observed over 10 years [7]. There is no universally accepted classification system of central airway complications after lung transplant. Four classification systems for airway complications after lung transplant have been published in recent years [8–11]. The major risk factors are immediate postoperative ischemia of the donor bronchi, length of the donor bronchi, surgical technique used, presence of microbial agents before the transplant in the recipient and donor bronchi, postoperative infections, postoperative mechanical ventilation, and use of immunosuppressant agents [12–14] A recent study published by our group demonstrated that bronchial complications after lung transplantation were associated with primary lung graft dysfunction and specific surgical techniques [7].A reduction in the frequency of post-transplantation bronchial complications was obtained by improving transplant preservation techniques and donor/recipient screening. The most common complication that may require endoscopic treatment is the presence of bronchial stenosis, followed by bronchial dehiscence, obstructive granulomas, bronchomalacia, bronchial fistulae, and endobronchial infections [15].

Bronchial stenosis generally occurs between 2 and 9 months after the surgical period, typically after extensive necrosis, dehiscence, and *Aspergillus* infections [6]. However, there are sometimes no previously documented lesions before the development of bronchial stenosis, which can be observed at the site of the anastomosis and also in the bronchi distal to the anastomosis, with or without anastomotic stenosis. A higher prevalence of distal stenosis located at the bronchus intermedius has been described, causing complete occlusion in nearly 2% of cases, otherwise known as the "vanishing bronchus intermedius syndrome" [16–19]. The clinical and functional impact of central airway stenosis (CAS) after lung transplantation, however, has never before been reported.

Material and Methods

Study design

We performed a retrospective analysis of patients who underwent lung transplantation at our institution between June 1, 2009 and August 31, 2014, enabling a significant follow-up. The study was approved by the Institutional Review Board of the French learned society for respiratory medicine –"Société de Pneumologie de Langue Française" (CEPR no 2018-003). To qualify for inclusion, all patients had to present: 1) a bilateral lung transplantation; 2) at least 1 post-transplant follow-up visit and endoscopic test to verify the presence or absence of bronchial stenosis; and 3) a post-transplant survival time of >3 months. The choice of June 2009 as the beginning of our study is related to modifications to our immunosuppressive protocol for basiliximab as induction therapy followed by tacrolimus, mycophenolate mofetil (MMF), and steroids, to obtain a homogeneous cohort in terms of immunosuppressive regimen. Since we wanted to compare pulmonary function tests, patients who had received single-lung transplants and cardiopulmonary transplants were excluded.

The same surgical team performed the lung transplantations throughout the whole study period. Before June 1st, 2012, the technique consisted of trimming the donor bronchus down to 1 cartilaginous ring above the first bronchial division. From June 1st, 2012, we modified our surgical technique [7]: the anastomosis of the right main bronchus was performed more distally by wedge excision of the proximal-medial part of the bronchus intermedius, and on the left, the main bronchus was shifted further down to the lobar bifurcation. The anastomoses were sewn with a single suture of absorbable monofilament and covered with the surrounding fat tissue from the donor.

The main characteristics analyzed were age, sex, smoking status, and indication for lung transplantation. Other parameters considered were pre-transplantation body mass index (BMI) and cytomegalovirus (CMV) status of donor and recipients. The correlation between CAS and postoperative lung function and overall survival was evaluated. Respiratory function tests were evaluated at 1, 6, 12, and 18 months after transplantation. We recorded forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and FEV1/FVC ratio. We also analyzed the respiratory infection rate and length of hospitalization for any cause after lung transplant, acute rejection episodes, chronic rejection during the post-transplantation follow-up, and grade of dyspnea at 18 months. Bronchial endoscopy evaluation was

routinely performed at 24 h, 1 month, and 1 year following lung transplantation, or after clinical indication (lung function deterioration, significant respiratory infections, or respiratory symptoms such as dyspnea).

We chose to evaluate only bilateral lung transplant recipients to avoid any possible underestimation of bronchial stenosis incidence and of the lung function tests related to unilateral transplantation. We excluded recipients who died in the first 3 months after lung transplantation to avoid evaluating patients with early deaths either not related to bronchial stenosis or too early to be related to the development of this type of complication. The cut-off point of 3 months was chosen as per previous studies to separate "early" and "late" airway complications.

Objectives

The main objective of our study was to evaluate the impact of CAS after lung transplantation on lung function tests. Secondary endpoints were the incidence of respiratory infections and acute rejection episodes, hospitalization length, and mortality. For respiratory infections, we only considered severe episodes that required hospitalization.

Central airway stenosis

We included all patients whose transplantation dated back to at least 3 months and presented with bronchial stenosis of stricture or malacia, at anastomotic or non-anastomotic sites (main or lobar bronchi), with a smaller diameter than that of the fiberscope caliber (Olympus BFQ™ 180, 5.1 mm), regardless of the presence of respiratory symptoms or impact on lung function tests. All patients were treated endoscopically at least once by a multimodal approach. Balloon dilatation was usually the first intervention performed, although multiple procedures were often necessary. In cases involving symptomatic and recalcitrant CAS, we used bronchial stenting by means of silicon stents or covered self-expanding metal stents (Novatech® GSS™, Tracheobronxane™ Dumon® or Aerstent®, Leufen Medical GmbH, Berlin, Germany). Occasionally, we treated CAS using electrocautery, laser, or dilatation with rigid bronchoscopy. Stents were removed in case of obstruction by tissue granulation, recurrent mucus plugging infections, or when no longer useful.

Statistical analysis

Qualitative variables are expressed as percentages and continuous variables as means (± standard deviation [SD]) or medians (interquartile range), as appropriate. Comparisons of qualitative variables were performed using the chi-squared test and continuous variables with the *t* test or Wilcoxon-Mann-Whitney
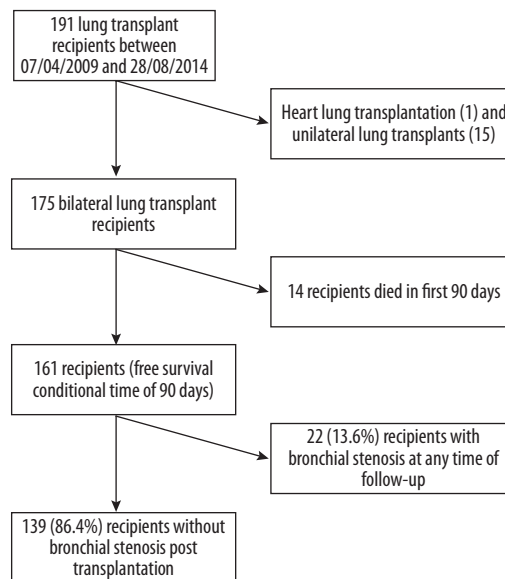

191 lung transplant recipients between 07/04/2009 and 28/08/2014

Heart lung transplantation (1) and unilateral lung transplants (15)

175 bilateral lung transplant recipients

14 recipients died in first 90 days

161 recipients (free survival conditional time of 90 days)

22 (13.6%) recipients with bronchial stenosis at any time of follow-up

139 (86.4%) recipients without bronchial stenosis post transplantation

Figure 1. Flow chart of the study.

U test, according to the distribution (Shapiro-Wilk test). For analysis of lung function tests at 1, 6, 12, and 18 months, we used repeated-measures ANOVA with Bonferroni correction for multiple comparisons. Survival analyses are presented as Kaplan-Meier curves. For all tests, the statistical significance threshold was set at $p < 0.05$. Figures and statistical analyses were performed using R studio software with the packages "ggplot2" and "stats" (Bioconductor software suite).

Results

A total of 191 patients underwent lung transplantation during the recruitment period. Of them, 175 (93%) underwent bilateral lung transplantations, 15 (7%) had single-lung transplantations, and 1 had a cardiopulmonary transplantation. There were 14 (8%) deaths in the first 3 months following lung transplantation, and these patients were removed from the evaluation of primary and secondary endpoints. A total of 161 remaining patients were evaluated in our cohort analysis (Figure 1). Their detailed characteristics are presented in Table 1.

Of these 161 remaining patients, 22 (13.6%) exhibited developing bronchial stenosis requiring endoscopic treatment during the follow-up. CAS was diagnosed at a median time of 98 days after transplantation (interquartile range: 78–115). No new case of CAS was detected at or after the 1-year systematic follow-up bronchial endoscopy. Nine patients (41%) presented bilateral stenosis, 7 (32%) had right-sided bronchial stenosis, and 6 (25%) had left-sided stenosis. Among these 31 CAS cases, 3 were characterized by predominant malacia.

Table 1. Characteristics of patients.

	Central airway stenosis				p
	No (*n*=139)		Yes (*n*=22)		
Age (years)	54	[33–60]	52	[33–56]	0.57
Gender (men)	79	(56.8)	14	(63.6)	0.71
Disease (%)					
CF	38	(27.3)	6	(27.3)	
COPD	60	(43.2)	11	(50.0)	
IPF	18	(12.9)	1	(4.5)	0.74
PPH	3	(2.2)	0	(0.0)	
Others	20	(14.4)	4	(18.2)	
Pre-LTx BMI (kg/m^2)	19.9	[17.4–23.8]	20.4	[19.0–22.7]	0.70
CMV status (%)					
D+/R+	39	(28.1)	11	(50.0)	
D+/R–	31	(22.3)	6	(27.3)	
D–/R+	39	(28.1)	3	(13.6)	0.10
D–/R–	30	(21.6)	2	(9.1)	
Pre-LTx steroids (%)	31	(22.3)	5	(22.7)	0.92
Smokers (%)	34	(24.5)	5	(22.7)	0.97
High Emergency (%)	14	(10.1)	3	(13.6)	0.89
Outcomes					
Hospitalization length (days)	75	[46–124]	114	[57–188]	0.048
Infection (% of pts)	92	(66.2)	20	(90.9)	0.036
AR (% of pts)	54	(38.8)	11	(50.0)	0.45
BOS (% of pts)	25	(18.0)	6	(27.3)	0.46

Data are expressed as median [range] or number (%). CF – cystic fibrosis; COPD – chronic obstructive pulmonary disease;
BMI – body mass index; IPF – idiopathic pulmonary fibrosis; LTx – lung transplantation; CMV – cytomegalovirus;
High Emergency – French allocation system for priority lung allocation; AR – acute rejection; BOS – bronchiolitis obliterans syndrome;
PPH – primary pulmonary hypertension; D – donor; R – recipient.

All the patients who exhibited developing bronchial stenosis were treated in the 1st year post-transplantation, using bronchial balloon dilatation (CRE pulmonary balloon dilator, Boston scientific, Marlborough, MA 01752, USA) in at least 1 session, with a maximum of 18 sessions of bronchial endoscopy necessary for 1 subject. Nine patients (43%) were treated by endobronchial stenting (Figures 2, 3).

Respiratory function tests (Table 2) revealed progressive improvement over the 18 months post-transplantation in patients without CAS, versus continued stability of FEV1 in the group with CAS (Figure 4). FVC increased steadily in both groups during follow-up. As a consequence, FEV1/FVC ratio (Figure 5) remained stable in recipients without CAS; in the stenosis group, we observed progressive decline in the FEV/FVC ratio, with the development of an obstructive ventilatory pattern. At 18 months post-transplant, patients with CAS had an FEV1/FVC of 61±14%, with a mean FEV1 that was 0.61 L lower than in patients without CAS. In some cases of unilateral stenosis, the flow-volume curve displayed a biconcave shape (Figure 6).

Respiratory infection episodes were significantly increased in the group with bronchial stenosis. During follow-up, 92 (66%) patients in the group without CAS had at least 1 hospitalization, compared to 20 (91%) in the CAS group (p=0.036). Length of hospitalization for any cause was also increased in lung transplant recipients who developed CAS: we found an average of 144±109 days in patients with CAS, compared to
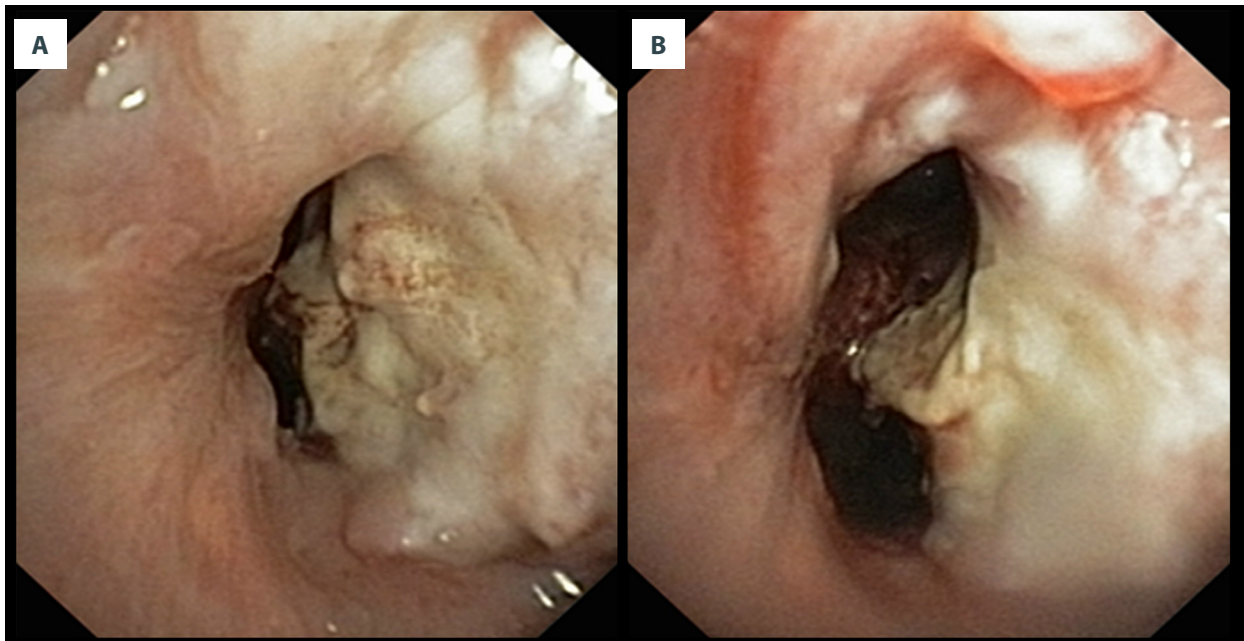
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Figure 2. (**A**) Endoscopic view showing an inflammatory irregular stenosis severely reducing the caliber of the right mainstem at the site of anastomosis. (**B**) Endoscopic view at the same level, after bronchoscopic dilatation with a balloon, showing the inlet of the right upper lobe bronchus above the inlet of the bronchus intermedius.
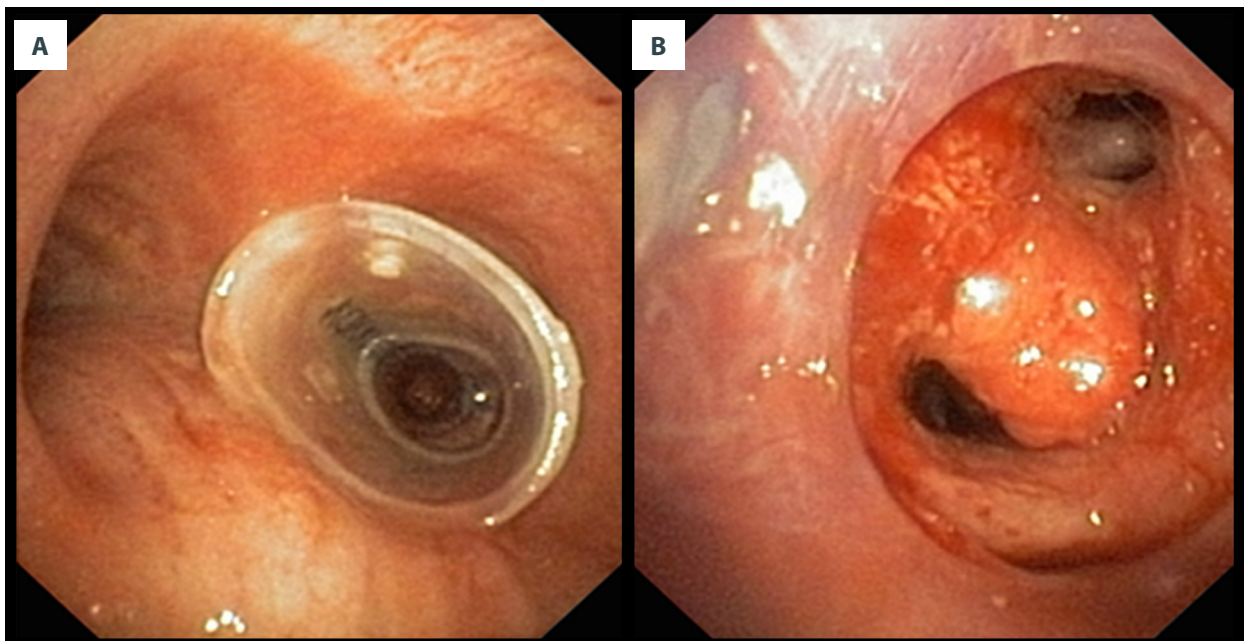

Figure 3. (**A**) Endoscopic view from the trachea after placement of an OKI silicone stent (NOVATECH® GSS™, La Ciotat, France). This stent was developed as a variant of a Y-Stent by Dr. Masahide Oki (Nagoya Medical Center, department Dr. Saka), and designed for stenting the right main stem bronchus around the firth of the right upper lobe and the bronchus intermedius. (**B**) Endoscopic view from inside the OKI stent to the middle lobe and lower lobe bronchi separated by a severely thickened inflammatory carina.

103±83 days in the other group (p=0.042). At 18 months after transplantation, the majority of patients with or without CAS did not complain of significant dyspnea during exercise: about 80% of the patients in the 2 groups had grade 0 dyspnea on the modified Medical Research Council dyspnea scale.

Table 2. Respiratory function tests at 1, 6, 12, and 18 months

Tests	Central airway stenosis		OR (95% CI)	p*
	No (n = 139)	Yes (n = 22)		
FEV1 (Liter)				**0.01**
M1	1.85±0.60	2.00±0.49	2.3 (0.7 to 8.0)	
M6	2.38±0.69	2.10±0.53	0.6 (0.2 to 1.5)	
M12	2.56±0.70	2.10±0.61	0.4 (0.1 to 1.0)	
M18	2.57±0.76	1.96±0.60	0.4 (0.1 to 1.0)	
FVC (Liter)				**0.75**
M1	2.14±0.75	2.33 (0.59)	2.8 (1.0 to 8.2)	
M6	**2.89±0.76**	**3.16 (0.73)**	**2.5 (1.2 to 6.0)**	
M12	3.17±0.75	3.21 (0.62)	1.6 (0.7 to 3.8)	
M18	3.20±0.82	3.23 (0.75)	1.6 (0.7 to 3.8)	
FEV1/FVC (%)				**<0.001**
M1	87±11	87±8	1.0 (0.9 to 1.1)	
M6	**82±13**	**67±10**	**0.91 (0.87 to 0.95)**	
M12	**81±12**	**65±12**	**0.91 (0.86 to 0.95)**	
M18	**81±13**	**61±14**	**0.92 (0.87 to 0.96)**	
FEV1 (% best)				**0.007**
M1	**69±17**	**83±11**	**1.07 (1.03 to 1.11)**	
M6	89±10	87±10	1.0 (0.96 to 1.05)	
M12	94±10	89±17	0.97 (0.93 to 1.02)	
M18	95±15	84±19	0.98 (0.95 to 1.01)	
FEV1 (% predicted)				**0.002**
M1	62±18	56±20	0.98 (0.95 to 1.01)	
M6	78±22	66±15	0.97 (0.95 to 1.00)	
M12	**84±22**	**67±14**	**0.96 (0.93 to 0.99)**	
M18	**84±23**	**62±22**	**0.96 (0.94 to 0.99)**	
Best FEV1 <1 year	2.66±0.70	2.40±0.52	0.6 (0.2 to 1.5)	

Data are expressed as mean ± standard deviation. FEV1 – forced expiratory volume in one second; FVC – forced vital capacity; OR – odds ratio; CI – confidence interval. * p value of repeated measures ANOVA with Bonferroni corrections for multiple comparisons.

We also considered the association of bronchial stenosis and acute rejection episodes: 65 patients out 161 (40%) presented at least 1 episode confirmed by histopathological diagnosis during the follow-up. In particular, 6 patients (3%) presented 2 episodes, 2 (1%) presented 3, and the remaining recipients had only single episodes. We found no significant association between bronchial stenosis and acute rejection. During the follow-up period, 25 of the non-CAS patients (18%) developed

bronchiolitis obliterans syndrome (BOS), compared to 6 (27%) in the CAS group. No patient experienced a restrictive chronic lung allograft dysfunction.

By observing the Kaplan-Meier survival curves (Figure 7) of patients with or without CAS (conditional on survival to 3 months), no significant difference seems to exist between the curves, which furthermore show a crossing. The 1000-day survival
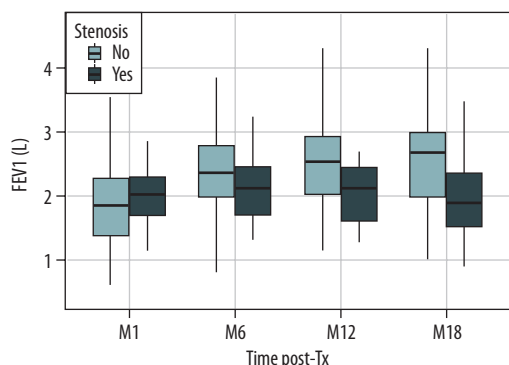
Figure 4. Boxplot of forced expiratory volume in 1 second (FEV1) at different periods of time, showing a progressive improvement of FEV1 in the group of lung transplanted patients who did not develop a central airway stenosis during the follow-up, compared with relative stability in the group with central airway stenosis (not significant). M1, M6, M12, M18: 1, 6, 12, and 18 months after transplant, respectively.
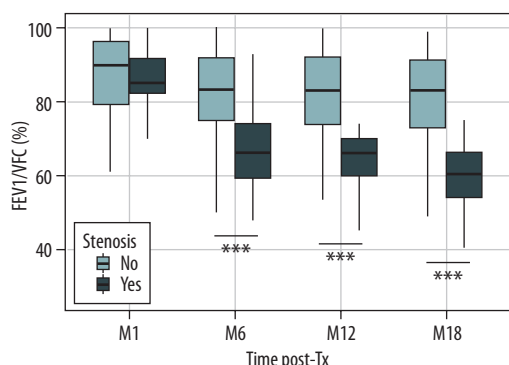

Figure 5. Forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) ratio in both groups (with and without central airway stenosis) at 1, 6, 12, and 18 months after lung transplantation. *** p<0.001. Patients in the group with central airway stenosis demonstrated early and persistent airflow limitation despite bronchoscopic multimodality treatment.

was 88.5±2.8% for the non-CAS group and 90.2±6.6% for others (NS). The log rank test and alternative tests (generalized Wilcoxon and Tarone-Ware) showed non-significant results.
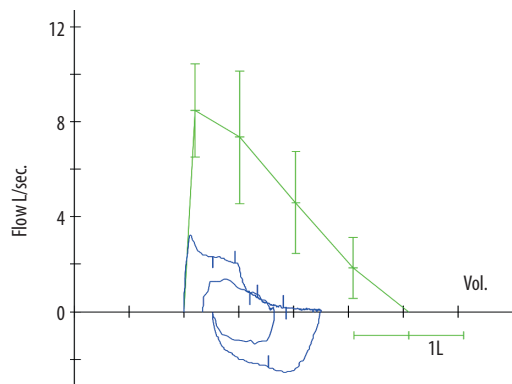

Figure 6. Example of a biconcave flow-volume loop in a patient with a bilateral lung transplantation complicated by unilateral CAS. In this case, it can be suggested that the lung with normal central airways empties and fills more rapidly than the lung with CAS.
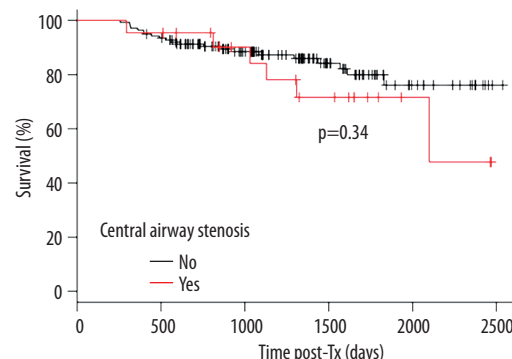

Figure 7. Kaplan-Meier survival by groups with or without post-transplant central airway stenosis conditional on survival to 3 months (n=161), showing no significant difference.

Discussion

Bronchial stenosis has been a major cause of comorbidity and mortality since the very first experiments with lung transplantation, and is still a frequent complication in the literature. The prevalence of central airway complications varies widely depending on the reporting system. The prevalence of this type of complication is high, reaching up to 33% if all patients with abnormal findings by routine bronchoscopy were reported regardless of need for intervention or associated symptoms. On the other hand, if the reporting system counts only the airway complications that are associated with symptoms, the prevalence of central airway complications is relatively low. The prevalence of CAS requiring endoscopic treatment was 13.6%

in our study. According to different studies [4–8], between 9% and 13% of patients developed anastomotic strictures severe enough to require endoscopic treatment.

In our study, lung function tests revealed a different course in recipients who developed CAS from those who did not. In the group of patients without CAS, mean FEV1 increased steadily while mean FEV1/FVC remained largely over 80%, reflecting a normal ventilatory pattern for most of the patients during the 18-month follow-up period. Conversely, patients with CAS developed progressive airflow limitation characterized by increased FVC, inability to improve their FEV1, and decreased FEV1/FVC ratio as a result. It must be emphasized that using the percentage of best FEV1 (average of the 2 highest postoperative values), as recommended by the International Society for Heart and Lung Transplantation, may not correctly reflect the impact of CAS. It can be difficult based on pulmonary function tests alone to differentiate the effect of CAS from the occurrence of BOS. However, CAS generally begins soon after transplantation, whereas BOS occurs later on, up to 1 year or even more, following transplantation. Furthermore, the aspect of the flow-volume loop can help differentiate CAS from BOS, as mentioned elsewhere [6]. As an example, Figure 6 shows a biconcave loop in a patient with a bilateral lung transplantation complicated by unilateral CAS, suggesting that the lung with normal central airways empties and fills more rapidly than the lung with CAS.

We did not assess the consequences of the persistent airflow limitation in patients with CAS on quality of life. However, it does not seem that lung function impairment translated into respiratory symptoms, since the same high proportion of patients ($\approx$ 80%) had no significant dyspnea (grade 0 mMRC) in the CAS group compared to the no CAS group.

We must assume that the difference in respiratory functional outcomes and rates of broncho-pulmonary infections between patients with CAS compared to those without is attributable to the persistence of bronchial stenosis, despite our multimodality endoscopic treatment. In our experience, respiratory infections and hospitalizations for any cause were both increased in patients with CAS. The relationship between CAS and broncho-pulmonary infections may be a two-way process. Different studies have in fact reported that early post-transplant broncho-pulmonary infections are a risk factor for CAS. On the other hand, CAS by itself and the presence of airway stents, which are foreign bodies, can also favor these infections. We also focused our attention on mortality related to post-transplantation CAS. Survival in our patients who

developed bronchial stenosis was not different compared to that of lung transplant recipients without CAS, although the small number of patients does not allow firm conclusions. Our findings differed to those of Hayanga [20], who found that increased mortality was correlated with airway complications in a large cohort collected retrospectively by the United Network for Organ Sharing data. However, they found lower prevalence of airway complications (1.4%), suggesting that only severe cases were reported in this registry. In a cohort of lung transplant recipients evaluated by Cho et al. [21], the prevalence of central airway complications was higher than in previous studies, rated at 39%, while CAS did not seem to affect lung function tests (data not shown). In this last study, bronchial complications were managed by either surgical or endoscopic means. They did not worsen the clinical outcomes of the lung transplant recipients and did not correlate with increased incidence of BOS. Finally, in the cohort of Duke University Medical Center evaluated by Shofer et al. [22], CAS affected 13% of lung transplant recipients, yet impacted neither survival nor BOS incidence. However, CAS was responsible for a substantial decline in spirometry before bronchoscopic treatment in 40% of patients (at least 200 mL loss of FEV1). Median FEV1 increased by 0.38 L in cases involving stent insertion and by 0.12 L with bronchoplasty alone.

Our study has a number of strengths as well as limitations, including its single-center and retrospective methodology. However, it is the largest study yet reporting the long-term evolution of lung function after CAS. It is still debatable if a different approach of endoscopic or surgical treatment could have led to better results, or, conversely, to more frequent complications [23]. It is possible that innovation in stent technology will enable better management of some difficult situations. For example, three-dimensional, computer-assisted customized airway stents [24] or biodegradable stents may help to treat complex CAS. Finally, we could not assess the impact of the impaired lung function in CAS patients on their quality of life.

Conclusions

CAS appears to not be a risk factor for mortality after lung transplantation if correctly managed with endoscopic treatment, yet it remains a cause of morbidity and deteriorating lung function.

Conflicts of interest

None.

References:

1. Wildevuur CR, Benfield JR: A review of 23 human lung transplantations by 20 surgeons. Ann Thorac Surg, 1970; 9: 489–515

2. Pearson FG, Goldberg M, Stone RM, Colapinto RF: Bronchial arterial circulation restored after reimplantation of canine lung. Can J Surg, 1970; 13: 243–50

3. Siegelman SS, Hagstrom JW, Koerner SK, Veith FJ: Restoration of bronchial artery circulation after canine lung allotransplantation. J Thorac Cardiovasc Surg, 1977; 73: 792–95

4. Ramirez J, Patterson GA: Airway complications after lung transplantation. Semin Thorac Cardiovasc Surg, 1992; 4: 147–53

5. Frye L, Machuzak M: Airway complications after lung transplantation. Clin Chest Med, 2017; 38: 693–706

6. Santacruz JF, Mehta AC: Airway complications and management after lung transplantation: Ischemia, dehiscence, and stenosis. Proc Am Thorac Soc, 2009; 6: 79–93

7. Olland A, Reeb J, Pyuraveau M et al: Bronchial complications after lung transplantation are associated with primary lung graft dysfunction and surgical technique. J Heart Lung Transplant, 2017; 36: 157–65

8. Shennib H, Massard G: Airway complications in lung transplantation. Ann Thorac Surg, 1994; 57: 506–11

9. Couraud L, Nashef SA, Nicolini P, Jougon J: Classification of airway anastomotic healing. Eur J Cardiothorac Surg, 1992; 6: 496–97

10. Chhajed PN, Tamm M, Glanville AR: Role of flexible bronchoscopy in lung transplantation. Semin Respir Crit Care Med, 2004; 25: 413–23

11. Thistlethwaite PA, Yung G, Kemp A et al: Airway stenosis after lung transplantation: Incidence, management, and outcome. J Thorac Cardiovasc Surg, 2008; 136: 1569–75

12. van Berkel V, Guthrie TJ, Puri V et al: Impact of anastomotic techniques on airway complications after lung transplant. Ann Thorac Surg, 2011; 92: 316–20

13. Van de Wauver C, Van Raemdonck D, Verleden GM et al: Risk factors for airway complications within the first year after lung transplantation. Eur J Cardiothorac Surg, 2007; 31: 703–10

14. Groetzner J, Kur F, Spelsberg F et al: Airway anastomosis complications in *de novo* lung transplantation with sirolimus-based immunuppression. J Heart Lung Transplant, 2004; 23: 632–38

15. Ruttmann E, Ulmer H, Marchese M et al: Evaluation of factors damaging the bronchial wall in lung transplantation. J Heart Lung Tranplant, 2005; 24: 275–81

16. Marulli G, Loy M, Rizzardi G et al: Surgical treatment of posttransplant bronchial stenoses: Case reports. Transplant Proc, 2007; 39: 1973–75

17. De Gracia J, Culebras M, Alvarez A et al: Bronchoscopic balloon dilatation in the management of bronchial stenosis following lung transplantation. Respir Med, 2007; 101: 27–33

18. Lari SM, Gonin F, Colchen A: The management of bronchus intermedius complications after lung transplantation: A retrospective study. J Cardiothorac Surg, 2012; 7: 8

19. Dutau H, Vandemoortele T, Laroumagne S et al: A new endoscopic standardized grading system for macroscopic central airway complications following lung transplantation: The MDS classification. Eur J Cardiothorac Surg, 2014; 45: e33–38

20. Awori Hayanga JW, Aboagye JK, Shigemura N et al: Airway complications after lung transplantation: Contemporary survival and outcomes. J Heart Lung Transplant, 2016; 35: 1206–11

21. Cho EN, Haam SJ, Kim SY et al: Anastomotic airway complications after lung transplantation. Yonsei Med J, 2015; 56: 1372–78

22. Shofer SL, Wahidi MM, Davis WA et al: Significance of and risk factors for the development of central airway stenosis after lung transplantation. Am J Transplant, 2013; 13: 383–89

23. Dutau H, Cavailles A, Sakr L et al: A retrospective study of silicone stent placement for management of anastomotic airway complications in lung transplant recipients: Short- and long-term outcomes. J Heart Lung Transplant, 2010; 29: 658–64

24. Guibert N, Didier A, Moreno B et al: Treatment of post-transplant complex airway stenosis with a three-dimensional computer-assisted customized airway stent. Am J Respir Crit Care Med, 2017; 195: e31–33