Long-Term Success of Metal Endobronchial Stents in Lung Transplant Recipients

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Abstract

Background Bronchial stenosis is a common complication following lung transplantation. We evaluated long-term associations of the use of self-expandable metal stents (SEMSs) with lung function tests, patient safety, and survival.

Methods A retrospective chart review of 582 lung transplantations performed at our institution between January 2002 and January 2018. Fifty-four patients with SEMSs (intervention group) were matched one-to-one to patients without SEMSs (control group) using propensity score matching for age, sex, the year, and type of transplantation (unilateral/bilateral), and underlying disease. Data regarding long-term lung function and survival were compared between the groups.

Results During a median follow-up of 54.8 months, the difference in survival between the study groups was not statistically significant ($p = 0.2$). Following 5, 7.5 and 10 years, values of mean forced expiratory volume in 1 second (FEV1) were comparable between patients with and without SEMSs as follows: 59.5 versus 62.6% ($p = 0.2$), 55.9 versus 55.0% ($p = 0.4$), and 63.5 versus 61.9% ($p = 0.3$), respectively. In the intervention group, a significant increase in the mean FEV1 was observed in 60 days after stent insertion (from 41.9 ± 12.8 to 49.5 ± 16.7% days, $p < 0.001$). Long-term complications following stent insertion included severe bleeding (1.8%), stent fractures (7.4%), stent stenosis (7.4%), stent collapse (3.7%), endobronchial pressure ulcer (1.9%), and stent migration (1.9%).

Conclusion SEMS insertion is associated with a positive sustained effect on lung function, without increasing long-term mortality. Thus, airway stenosis after lung transplantation can be safely and successfully treated using endobronchial metal stenting, with tight bronchoscopic follow-up and maintenance.

Keywords
- stents
- transplantation
- lung
- pulmonary function

Introduction

Bronchial stenosis is a common complication after lung transplantation, presenting in as many as 5 to 32% of all lung transplant recipients.[1–4] Stenosis occurs due to airway ischemia, necrosis, anastomotic dehiscence, or airway infection.[4–6] This complication may even arise in asymptomatic patients.[7,8] Laser ablation and balloon dilation may provide immediate

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relief of symptoms. However, these therapies are often plagued by recurrence; thus, endobronchial stent placement is frequently required as a more definitive solution.[4,9,10]

Few reports in the medical literature provide long-term safety outcomes following insertion of self-expandable metallic stents (SEMSs) in lung transplant recipients. Previous reports have shown that complications associated with stent insertion were due to bacterial colonization,[7] infections,[5,11] granulation overgrowth,[7] stent migration,[9,10] stent collapse,[4,12] metal fracture,[4,7] airway erosion, and hemoptysis.[13] In addition, stent removal might be costly and be further associated with its own set of complications.[14] Some authors have suggested that SEMSs offer excellent early palliation[13]; however, later complications might be more harmful than the initial obstructive process. Consequently, many lung transplant centers avoid using SEMSs.[2,15]

The aim of this study was to evaluate long-term lung function tests, patient safety, and mortality following the use of SEMSs.

Patients and Methods

Study Design

The study received our Institutional Review Board approval. We performed a retrospective single-center cohort study of lung transplantations performed at our medical center between January 2002 and January 2018. Death within 30 days of the lung transplantation was a criterion for exclusion from the study.

We matched the lung transplant recipients who underwent SEMS insertion one-to-one patients without SEMSs, using propensity score matching for age, sex, year of transplantation, type of transplantation (unilateral/bilateral), and underlying disease. We compared between the groups, long-term survival, and forced expiratory volume in 1 second (FEV1). For the intervention group, we also calculated complication rates and the rate of FEV1 improvement 60 days of poststenting. Rapid improvement was defined as achieving the peak of FEV1 up to 3 months of poststenting, while delayed improvement was defined as achieving this point at a later follow-up.

Bronchoscopic Procedure

During the study period, we attempted a conventional treatment to manage bronchial stenosis in all patients prior to the decision to place a stent. This included mechanical debridement, Nd:YAG Laser photo resection (Dronier peristaltic pump pp 1,800) and balloon dilatation (balloon dilatation catheter; CRE; Boston Scientific Corporation, Watertown, Massachusetts, United States). A stent was placed to maintain airway patency only when the residual stenosis was greater than 75%.

Before bronchoscopy, each patient underwent a standard preoperative assessment, including a physical examination, routine laboratory tests, spirometry, chest radiography, and a computed tomography scan of the chest. All bronchoscopic procedures were performed in our pulmonary institute. To provide analgesia and sedation, midazolam (1 mg) and fentanyl (0.5–1 µg) were administrated. Propofol (20–40 mg) was administered at intervals of 2 to 5 minutes if deemed necessary. The procedures were performed with supplemental oxygen via a nasal cannula. In all procedures, bronchoscopy was performed using a large working channel bronchoscope (Olympus Excera; BF-1TQ180 II video endoscope, Olympus, Tokyo, Japan). The stents that were used included SMART nitinol stent (Laser cut, single Nitinol tube, Cordis; Miami, Florida, United States) for an airway diameter above 10 mm, or PALMAZ (laser cut stainless steel slotted tube, Johnson & Johnson; New Brunswick, New Jersey, United States, and Interventional Systems; Warren, New Jersey, United States) for a diameter less than 10 mm. Stents were passed directly through the bronchoscope working channel. Direct vision was achieved by using bronchoscope and fluoroscopy (►**Fig. 1**).

Follow-up Protocol

Follow-up visits for all patients who received stents were at 1 month of poststenting, 3 months and then 6 months, thereafter until January 2018. Follow-up was done by detailed medical interview and physical examination, pulmonary function tests, and chest X-ray. The patients were given aerosol inhalation with 3% sodium chloride 2 to 3 times daily for the first month following stent placement. Bronchoscopy was

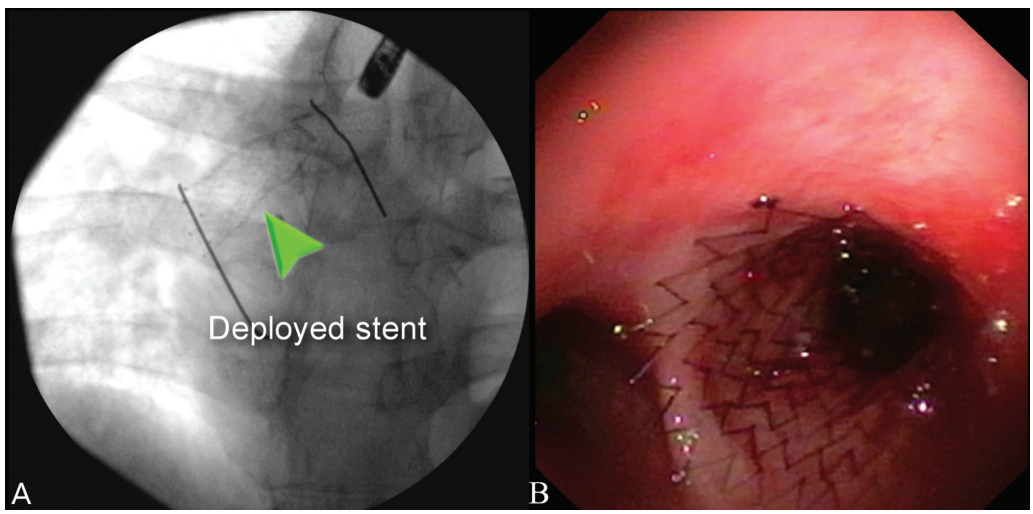

Fig. 1 Endobronchial stent placement in the right main bronchus. (**A**) Fluoroscopic view. (**B**) Bronchoscopic view.

performed every 3 to 6 months to clear secretions and remove granulation tissue growth within the stent. Unscheduled bronchoscopy was performed in the event of clinical deterioration, including worsening dyspnea, reduction in pulmonary function tests (i.e., a drop in FEV1 of more than 10%), or new significant findings on chest imaging, such as lobar atelectasis or nonresolved pneumonia.

Airway Complications

Airway complications after each follow-up visit for bronchoscopic maintenance were documented in the procedure reports. For the purpose of this study, we reviewed all the complications that occurred poststent insertion until the end of the follow-up period. These included the following: (1) severe purulent secretion, defined as more than 100 mL of purulent secretions on suction; (2) endobronchial bleeding, which was categorized into the following three groups: (a) mild bleeding, defined as limited bleeding such as mucosal bleeding, (b) moderate bleeding, defined as self-controlled bleeding that did not compromise the airway, and (c) severe bleeding, defined as bleeding that compromised the airway; (3) unscheduled bronchoscopy; (4) stent fractures; (5) polyps in stent growth; (6) stent collapse; (7) stent pressure ulcer; (8) stent malposition; (9) stent migration; (10) stent granulation tissue necrosis, which was categorized into the following three groups: (a) mild-to-moderate stenosis—endobronchial narrowing up to 50% of the bronchial diameter; (b) severe stenosis—more than 50% bronchial narrowing, and (c) complete stenosis—total blockage of the bronchus.

Statistical Analysis

The results were expressed as means and standard deviations for quantitative data and as numbers (percentages) of presented cases for qualitative data. Statistical comparisons were performed between the data obtained for the intervention versus control group. We used Chi-square test for comparison of categorical variables and Student's *t*-test for continuous variables as appropriate. We also used the paired *t*-test to assess the change in FEV1 before and after stent insertion. Survival estimates were provided using the Kaplan–Meier method. A *p*-values of < 0.05 was considered significant. Statistical analysis was performed using SAS software version 9.2 (SAS Institute Inc., Cary, North Carolina, United States).

Results

Establishment of the Intervention and Matched Control Groups

Of 665 patients who underwent lung transplantations at our medical center during the study period, 83 died within 30 days of the operation. Of the 582 remaining patients, 57 (9.8%) required the insertion of SEMSs due to symptomatic endobronchial stenosis diagnosed on flexible bronchoscopy. We were able to match 54 of these 57 patients, according to the criteria described above, such as to establish an intervention group and a control group, each comprising 54 patients.

Baseline Characteristics of the Intervention and Control Groups

Baseline characteristics of patients in the intervention and control groups are presented in ►**Table 1**. In the entire cohort, the mean age was 53.7 ± 12.0 years and 55.5% were males. In both study groups, the most frequent reasons for lung transplantation were pulmonary fibrosis and emphysema.

Follow-up Data for Patients from the Intervention Group

During a median follow-up period of 54.8 months (range: 1–170 months), a total of 63 SEMSs (61 SMART and 2 PALMAZ) were inserted in 54 patients. Thirty of the stents were placed into the right main bronchus and 33 into the left main bronchus. In seven patients, stents were removed and replaced by new ones due to the following complications: stent occlusion ($n = 4$), stent collapse ($n = 2$), and stent migration ($n = 1$). The respective mean and median periods from lung transplantation to the first stent insertion were

Table 1 Baseline characteristics of lung transplant recipients with and without endobronchial stents

Characteristics	Control group patients without stents ($n = 54$)	Intervention group patients with stents ($n = 54$)	*p*-Value
Age (y)	54.5 ± 11.6	52.9 ± 12.0	0.4
Male gender	30 (55.5)	30 (55.5)	1
Transplant type			1
One lung	37 (68.5)	36 (66.7)	
Double lung	17 (31.5)	18 (33.3)	
Main reason for transplantation			0.95
Pulmonary fibrosis	21 (38.9)	18 (33.3)	
Emphysema	17 (31.5)	17 (31.5)	
Cystic fibrosis	7 (13.0)	6 (11.1)	
Bronchiectasis	4 (7.4)	6 (11.1)	
Others	5 (9.2)	7 (13.0)	

Note: Data are expressed as means $\pm$ standard deviations or *n* (%) of presented cases.

286.7 ± 411.1 days and 163.5 days (range: 12–2,134). The respective mean and median periods to the second stent insertion were 772.2 ± 611.9 days and 578.0 days (range: 157–2,108).

Twelve of the patients (22.2%) in the intervention group had at least one episode of severe purulent secretions during bronchoscopic follow-up; these were treated with suctions and antibiotics when infection was suspected. Fourteen patients (25.9%) had at least one episode of endobronchial bleeding. Of these, eight had limited (mild) episodes, five had self-controlled bleeding (moderate), and one patient had severe bleeding, which necessitated mechanical ventilation after laser therapy. Eighteen patients underwent unscheduled bronchoscopy, due to various reasons: atelectasis ($n = 10$), unresolved pneumonia ($n = 6$), and an unexplained decline in lung function tests ($n = 2$). Four patients (7.4%) had small fractures at the edges of the stents during a follow-up of 119 to 1,196 days. The broken particles were safely removed by flexible bronchoscopy, without further complications. An additional two (3.7%) patients had polyp stent ingrowth that necessitated polyp removal by forceps. One patient developed an endobronchial ulcer 23 days of poststent insertion, which necessitated stent removal. Fifty-two patients (96.3%) had at least one episode of mild stent granulation and 14 (25.9%) had at least one episode of moderate granulation.

A significant increase in the mean FEV1 (from 41.9 ± 12.8 to 49.5 ± 16.7%, $p < 0.001$) was observed 60 days after stent insertion. The median time for reaching maximal FEV1 following stent insertion was 211 days, the range was 30 to 1,864 days. At this point, the median change in FEV1 was increased by 44.8%, ranging from 29.5 to 211.9%. In 29 patients, FEV1 showed rapid improvement after stent insertion (e.g., the patient in ►**Fig. 2A**). While in 25 patients, FEV1 showed delayed improvement (for example, the patient in ►**Fig. 2B**). Six of these 25 patients with slow recovery had evidence of a pulmonary infection (*Pseudomonas aeruginosa*) that necessitated antibiotic treatment. Of 25 patients who gradually improved, 14 had bilateral lung transplantation, and 11 underwent unilateral lung transplantation.

Outcomes Compared between the Intervention and Control Groups

The rates of chronic lung rejection for the intervention and control groups were 37.0 and 35.2%, respectively, $p = 0.8$. ►**Fig. 3** presents mean FEV1 values over time in the study groups. At 2.5 years of posttransplantation, the FEV1 values were significantly lower in the intervention than in the control group (53.5 vs. 66.1%, $p < 0.001$). However, the mean FEV1 values did not differ significantly between the intervention and control groups at 5, 7.5, and 10 years as follows: 59.5 versus 62.6% ($p = 0.2$), 55.9 versus 55.0% ($p = 0.4$), and 63.5 versus 61.9% ($p = 0.3$), respectively. A statistically significant difference in Kaplan–Meier survival curves was not observed between the study groups ($p = 0.2$; ►**Fig. 4**).

Discussion

This study demonstrated significant improvement in pulmonary function 60 days after endobronchial SEMS insertion. This rapid improvement in spirometry measures continued and reached a maximum at a median of 211 days of postbronchial stenting. Our results are consistent with previous studies that showed 17 to 87% improvement of FEV1 in the postendobronchial stenting period.[5,7,9,11] A maximum increase was reported at a median of 118 days of poststenting, with a final increase of 123% in FEV1.[5] Moreover, Kapoor et al found that lung function improved up to 6 months of poststenting,[12] and Burns et al reported that spirometry continued to improve even up to 1 year.[4]

We showed that for some patients, lung function improved rapidly after endobronchial stenting, while others needed a

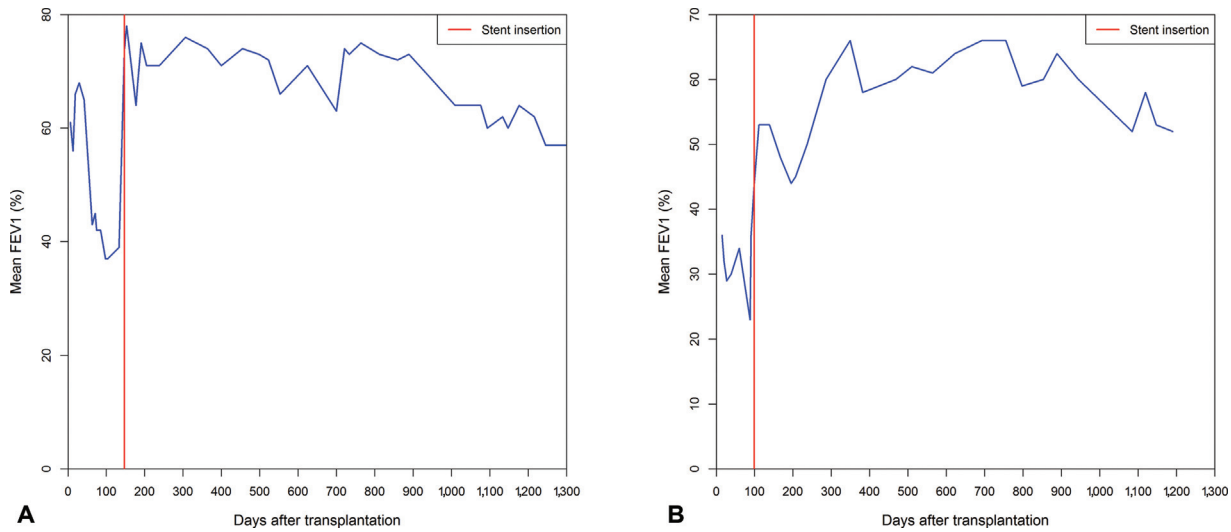

Fig. 2 The course of FEV1 changes after transplantation and stent insertion. (**A**) A patient with immediate improvement in FEV1 after endobronchial stent insertion. (**B**) A patient with delayed improvement in FEV1 after endobronchial stent insertion. The vertical red line represents the time of stent insertion. On the X-axis, time "0" represents the follow-up after lung transplantation. FEV1, forced expiratory volume in 1 second.

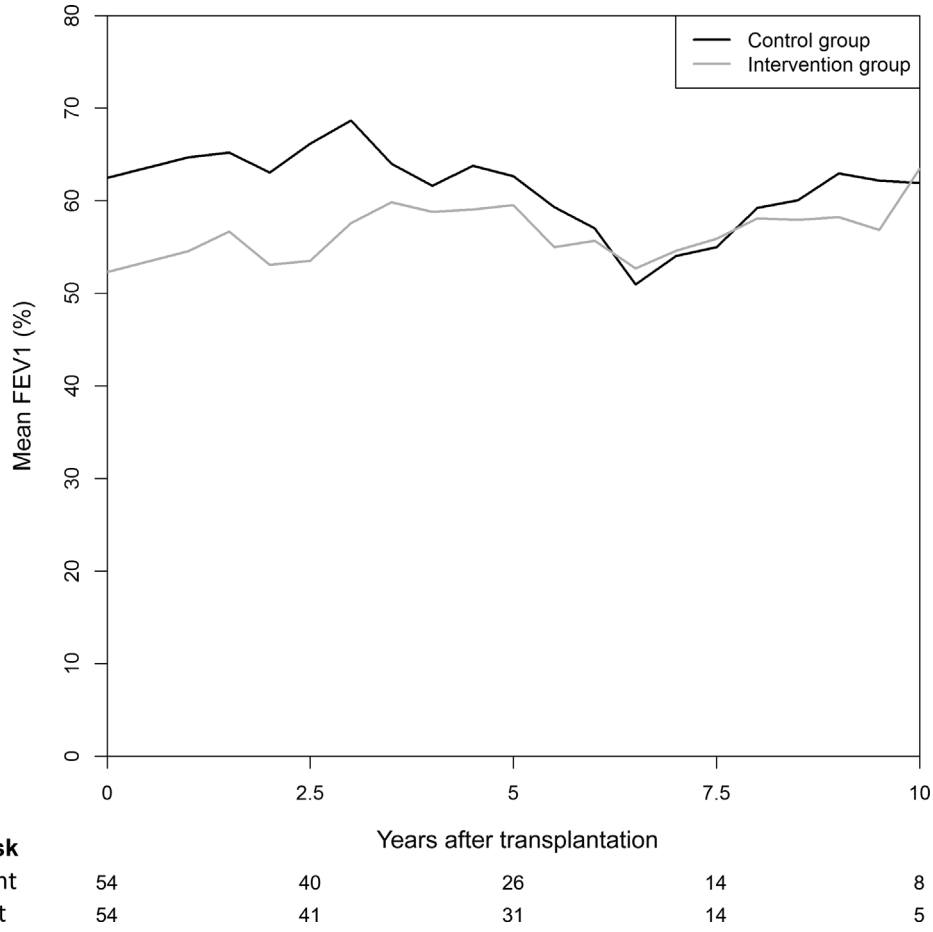

Fig. 3 Change in FEV1 in the intervention and control groups. On the X-axis, time "0" represents 30 days after lung transplantation for the intervention and the control groups. FEV1, forced expiratory volume in 1 second.

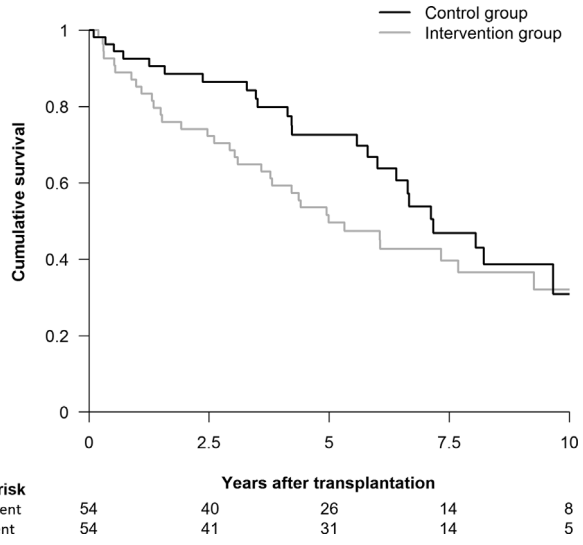

Fig. 4 Kaplan–Meier estimate survival curves. The difference in survival between the lung transplant recipients with stents (the intervention group) and the propensity-matched control group without stents was not statistically significant, $p = 0.2$.

longer period for improvement. We suggest several possible explanations for delayed improvement in lung function poststenting. Some patients had endobronchial stenosis-related pneumonia; and thus, recovery from the systematic and local infection sequalae took time. Others were referred to pulmonary rehabilitation that helped improve pulmonary function. Finally, bronchial inflammation and scarring after endobronchial ablation may require time for bronchial remodeling and gaining function.

This study also evaluated the long-term effects of SEMSs on lung function. We found lower lung function measurements in the first 2.5 years after lung transplantation in the intervention than in the control group. However, no significant differences in the mean FEV1 values were found between the groups during the 5 to 10 years of poststenting. The decreased lung function at 2.5 years of posttransplantation is apparently due to the occurrence of most of the stenosis events during this period (the mean durations were 286.7 ± 411.1 days for the first stent insertion and 772.2 ± 611.9 days for the second stent). This concurs with other studies that showed that bronchial stenosis can develop at any time following transplantation, yet most commonly occurs within the first year posttransplantation.[16,17] We assume that anastomotic stenosis in the early postoperative period is related to surgical technique, graft ischemia, and disruption of blood supply to the anastomotic area; while bacterial and fungal colonization or infection are factors that influence in the long term. Taken together, our findings demonstrate that SEMSs afford sustained improvement of lung function.

This study also adds information about endobronchial stenting complications. Comparing the complication rate with other studies is difficult due to inconsistent definitions. We calculated the percentage of patients who had at least one endobronchial complication, similarly to Gottlieb et al[7] and Chhajed et al.[10] Those studies found diverse percentages of stent migration (3 – 27%), mucous plugging (11 – 27%), and stent fractures (3 – 9%). Others calculated the number of complications relative to the number of procedures,[4] the number of months at follow-up,[12] or the number of anastomoses.[5] Notably, long-term infectious complications that have been reported in the medical literature and that we did not address in this study include pneumonia,[11] pseudomonas infection,[7] and aspergillus colonization.[5]

This study demonstrates that despite the development of stent-related complications in a proportion of patients, stent insertion is useful and does not increase mortality in a long-term follow-up. The medical literature is inconclusive regarding the impact of stent insertion on long-term survival of lung transplantation recipients. Our findings corroborate those of two other studies that reported similar survival rates with and without endobronchial stenting in lung transplant recipients.[5,8] An additional study even showed that stent placement may improve prognosis by 66% and reduce the risk of death compared with bronchoplasty alone.[9] However, a large study that included 706 patients with a median follow-up of 777 days showed reduced survival among lung transplantation patients who received an endobronchial stent.[7]

Our center has adopted an intensive bronchoscopic follow-up for all lung transplant recipients with SEMSs, for optimal management and for the prevention of stent complications. On average, we perform bronchoscopic examinations 1-month poststent placement and follow-up bronchoscopic examinations at least 3 to 6 months afterward. This approach enables early detection and treatment of complications, minimizes restenosis by degranulation therapy, and facilitates diagnosis of infection.

Over the past decade, the field of interventional bronchoscopy has increasingly addressed complications of bronchial stenosis. This progress is apparent in three aspects. First, new anastomotic techniques have been implemented, this is probably the most significant factor for effective anastomotic healing.[18] Second, the technique for endobronchial debridement presently includes balloon bronchoplasty, cryotherapy, laser photoresection, electrocautery, and high-dose endobronchial brachytherapy.[19] Third, the third-generation endobronchial stents are fully covered with synthetic material, which prevents ingrowth granulation tissue and subsequently precludes stent stenosis.[20]

Strengths and Limitations

A strength of this study is the large cohort of patients who underwent endobronchial stenting, spanning a long follow-up period. Further, the establishment of a propensity-matched control group enabled comparing patients with similar baseline characteristics. Limitations of the study include its retrospective, single-center design that focused only on metallic stent insertion.

Conclusion

Bronchial stenosis is not an uncommon complication following lung transplantation. Endobronchial stents have been shown to improve lung function in the short term and have a sustained effect over the long term. The lung function of some patients improves immediately poststenting, while others have delayed improvement. Stent-related airway complications can be safely treated with close follow-up. Continuous SEMS maintenance by scheduled follow-up bronchoscopy is essential to preserve stent patency and function. Endobronchial stent insertion was not shown to increase long-term mortality in lung transplant recipients. Finally, in our experience, the long-term complication rate of SEMSs in lung transplant recipients seems favorable with appropriate maintenance.

Conflict of Interest
None declared.

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