

Metallic stents for airway complications after lung transplantation: long-term follow-up

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Abstract

OBJECTIVES: Bronchial stenosis is still a significant source of morbidity and mortality following lung transplantation (LTX) and often mandating placement of a bronchial stent. It has been suggested that although self-expanding metal stents offer excellent early palliation, their long-term complication rates are unacceptably high, and hence, their usage in many transplantation centres has been nearly abandoned. The aim of the study was to assess short- and long-term complication rates and survival in LTX patients with bronchial stenosis treated with insertion of self-expanding metal stents.

METHODS: From January 1997 to March 2013, 435 patients underwent LTX (325 single-LTX and 110 bilateral LTX). Of 503 actual anastomoses at risk (derived by subtracting the number of anastomoses in 30 patients who died within 30 days of LTX), 60 airway complications (11.9%) in 47 patients required self-expanding metal stent insertion. We assessed the early results and long-term outcomes and survival compared with LTX patients in whom stents were not required.

RESULTS: The median follow-up period ranged from 1 to 132 (median 54) months. Immediate relief of symptoms was achieved in the vast majority of patients (95%). One-, three- and five-year survival in patients who required self-expanding metal stent placement were 77.7, 66.6 and 55.5%, respectively. The corresponding survival rates in LTX patients without stents were 69, 64.9 and 61.1% ($P > 0.05$).

CONCLUSIONS: Self-expanding metal stents are safe and effective tools in the management of airway complications post-LTX and provide immediate improvement in symptoms and pulmonary function tests in the vast majority of cases. The long-term complication rate is low, and mortality is similar to that in LTX patients who did not require stent insertion.

Keywords: Metallic stent • Lung transplantation • Airway stenosis

INTRODUCTION

The reported incidence of airway complications following lung transplantation (LTX) varies widely and ranges between 1.6 and 33%; however, most centres report an average complication rate of 7–18% [1, 2]. Bronchial stenosis is the most common airway complication and it is usually seen following necrosis, anastomotic dehiscence healing or airway infections. Two patterns of bronchial stenosis have been described: the first and most common is at the surgical anastomosis site and the second a more distal bronchial narrowing referred to as segmental non-anastomotic bronchial stenosis. Segmental non-anastomotic bronchial stenosis is rare with an estimated incidence of ~2.5–3%. Clinically, bronchial stenosis may be asymptomatic or may present with declining expiratory flows, variable of fixed intrathoracic obstruction, dyspnoea, cough or post-obstructive pneumonia. Although the improvement in surgical techniques and increasing experience has significantly reduced the incidence of such complications, they continue to pose a major therapeutic challenge [2–10].

Flexible bronchoscopy remains the gold standard for the diagnosis and treatment of bronchial stenosis following LTX and several endoscopic techniques, including balloon bronchoplasty, laser and stent placement, were used, with variable success rates [2–10]; stent placement is occasionally required to maintain a patent airway. Following stent placement, immediate improvement in symptoms and flows is reported in up to 90% of cases, whereas long-term improvement of symptoms in ~50% of patients is expected [6–10].

A variety of different stent models have been commercially available over the last 20 years. Silicone stents are used in post-lung transplant patients and are a safe and effective mode for the management of anastomotic complications, although, associated with common stent-related complications such as obstructive granulation, mucus plugging and migration [11, 12]. A major drawback of silicone stents is that their placement requires the use of rigid bronchoscope and general anaesthesia.

Self-expandable metal stents (SEMSs) have several advantages over silicone stents. SEMS can be placed by fiberoptic bronchoscopy (FFB) using fluoroscopic guidance [13–16]. In addition, these

stents can be placed more distally in the tracheobronchial tree, thus avoiding the occlusion of main branch airways. The use of the early models of airway stents (Gianturco stents) was associated with an unacceptably high rate of migration on the one hand, and difficulty in removal on the other hand. Migration is rare in the modern types of stents, currently used. Compared with silicone stents, metal stents have a larger internal-to-external diameter ratio and are less likely to migrate [10–14]. Concerns regarding long-term complications of SEMs for benign airway diseases have been raised [17, 18]. Previous reports have shown an overall 54% incidence of complications, of which 16–33% are due to infection, 12–36% due to granulation tissue formation and 5% due to stent migration [10–17]. Other complications include halitosis and metal fatigue. It has been suggested that although SEMs offer excellent early palliation, their late complications may be worse than the initial obstructive process, and hence, many LTX centres have abandoned their use. To investigate this troubling concept, we evaluated both the short- and the long-term outcomes of SEMs placed in large-cohort LTX patients.

MATERIALS AND METHODS

Our institute has been serving as the sole referral centre for LTX in Israel since 1997, with an average annual rate of 50 transplantations per year. We retrospectively analysed the medical records of all patients who underwent LTX between January 1997 and March 2013, and who underwent SEMs insertion. All patients provided informed written consent for bronchoscopy, and the study has been approved by the local ethics committee (IRB approval number: 6337). The surgical approach for single-LTX was an anterolateral thoracotomy and for bilateral sequential LTX, bilateral trans-sternal anterior thoracotomy (clamshell incision). For organ preservation, Perfadex (Vitrolife, Sweden) was used. We are also using retrograde flush with Perfadex at the time of the back-table preparation. The mean ischaemic time was 150 min for single-LTX and 210 min for double-LTX. Cardiopulmonary bypass (CPB) was used in 20% of patients and the mean CPB time was 110 min.

The technique for bronchial anastomosis was as follows. Absorbable suture material polydioxanone (PDS, Ethicon, Inc., NJ, USA) was used. A continuous suture of the membranous wall (PDS, 4/0) and end-to-end anastomosis with interrupted single sutures (PDS, 3/0) of the cartilaginous part was performed. The first suture to unite the cartilaginous parts was placed in the middle of the circumference to achieve optimal size matching. In none of the patients, a viable tissue patch was used.

The patients received regular triple immunosuppressive therapy with tacrolimus, mycophenolate mofetil and prednisone combined with prophylaxis against *Pneumocystis carinii*, cytomegalovirus CMV and fungal infections. Each patient underwent a standard post-operative assessment, including physical examination, routine laboratory tests and spirometry every 3 months. Chest computed tomography was performed every 6 months. In addition, FFB was routinely performed 3, 10 and 30 days following the operation and whenever a clinical indication was encountered. FFB was performed under conscious sedation with midazolam (1–10 mg) and alfentanil (0.5–1.5 mg), in the bronchoscopy suite and under spontaneous ventilation with supplemental O₂ through nasal cannula. The equipment used included flexible bronchoscopes (Pentax Co., Tokyo, Japan or Olympus Co., Tokyo, Japan). In patients with bronchial stenosis, the initial treatment included balloon dilatation and/or laser photo-resection. A combination of clinical symptoms

consistent with airway obstruction (increasing cough, recurrent infections and dyspnoea) deteriorating lung function and endoscopic confirmation of airway stenosis was required before stenting was considered.

When clinically indicated, uncovered SEMs was inserted under conscious sedation using fluoroscopic guidance (SMART nitinol stent, Cordis, Miami, FL, USA or Wallstent, Boston Scientific Corp.; Natick, MA, USA).

Insertion of stents was performed under conscious sedation with fluoroscopic guidance by two of the authors (Mordechai R. Kramer and Oren Fruchter) as previously described [19]. With the aid of radiological screening, the points at which the stenosis begins and ends are marked on the skin surface with metallic skin marks. This is performed by placing the skin marks while the tip of the bronchoscope is first at the proximal end of the stenosis and then at the distal end. The skin marks are placed vertical to the tip of the bronchoscope, and the measured distance between marks represents the desired length of the stent. The types of stents were chosen according to the length and diameter of bronchial stenosis. In addition, in cases of tortuous airway, SMART stent was chosen since it tends to fit more comfortably within the airway than the stiffer Wallstent stent. Chest radiographs were performed on the same day or following day to evaluate stent position. Spirometry data were collected directly before and 30 days after stent placement. All lung transplant recipients received frequent, individual, centre-based, life-long follow-up care. Patients were usually seen in our out-patient clinic every 12 weeks. In the case of acute unexplained respiratory symptoms, prompt attendance at our follow-up clinic was arranged. In the case of symptoms, functional impairment or radiological abnormalities, repeat FOB was performed. Patients in whom SEMs was inserted, underwent follow-up FFB at 6 weeks and every 3 months thereafter, to maintain stent patency.

Definitions

We used the definitions set by Gottlieb *et al.* [17] as follows. Successful treatment was defined as improved clinical symptoms and/or an forced expiratory volume at 1 s (FEV₁) increase of ≥10% from the pre-treatment level. Restenosis was defined as the inability to pass a standard 4.9 mm bronchoscope (Pentax –15, Pentax, Tokyo, Japan, or BF-P180; Olympus, Tokyo, Japan). Complications were defined as early in stent-related clinical events occurring ≤30 days after insertion, with late complications relating to any event thereafter.

Statistical analysis

Descriptive data are presented as mean (±SD) or median (range). Survival curves of patients with and without stents were evaluated and compared by plotting Kaplan–Meier curves. Statistical analyses were performed using a statistical software package (MedCalc Version 9.3.0.0, USA).

RESULTS

Between January 1997 and March 2013, 435 patients underwent LTX. The study group series consisted of bilateral sequential LTX (*n* = 110) and single LTX (*n* = 325) for a total of 545 potential anastomoses at risk. Early mortality (30 days) in our cohort was 6.9% (of

30 patients, 12 patients with bilateral sequential LTX and 18 with single LTX, leaving a total of 503 actual anastomoses at risk. In those patients, 60 airway complications in 47 patients required SEMS insertion (11.9%). Of those 47 patients in whom SEMS were placed, in 2 patients three stents were required, in 9 patients two stents were placed and in the remaining 36 patients a single SEMS was inserted. The indications for LTX in these patients were: cystic fibrosis ($n = 5$), emphysema ($n = 16$), pulmonary fibrosis ($n = 12$), pulmonary hypertension ($n = 2$) and other indications ($n = 12$). All patients who required SEMS placement presented with signs and symptoms of airway obstruction including shortness of breath, cough, effort dyspnoea and wheezing. SEMS were placed following a median period of 159 days post-transplantation (range 15–2160 days). SEMS was placed in the right main stem bronchus ($n = 28$), in the left main stem bronchus ($n = 30$), in the lingular bronchus ($n = 1$) and in the left upper lobe bronchus ($n = 1$). In our series, none of the SEMS was placed due to non-anastomotic stenosis.

No immediate significant complications were associated with the SEMS insertion procedure. Two patients developed short-term fever that responded to antibiotics and 1 had haemoptysis that resolved spontaneously. No patient required operative intervention following the procedure.

Immediate relief of symptoms was achieved in the vast majority of patients (95%). Functional improvement was immediate with a mean FEV₁ gain of 25%. A representative case of a 53-year old patient with emphysema who underwent left LTX and developed severe bronchial stenosis 9 months following LTX that was relieved by SEMS placement is presented in Figs 1 and 2. The overall granulation tissue formation rate mandating treatment with mechanical debridement or laser to prevent restenosis was 65%. We noted no differences between SEMS types with respect to the complications associated with them and the resulting indication for removal. In 6 (6%) patients, the SEMS had to be removed due to excessive granulation tissue formation. The average age was 60.2 years, and the average time from SEMS placement to retrieval was 30 (range 16–48) months. The indication for removal of the stent was excessive granulation formation and refractory stenosis of the bronchial lumen. All retrieval procedures were done by flexible bronchoscopy under moderate sedation via the trans-oral approach using a bite-block. The average procedure time was 25

(range 12–65) min. In 2 cases, endotracheal tube was inserted electively to facilitate the oral removal of the stent by the flexible bronchoscope forceps.

During a median follow-up period of 54 (range 1–132) months, 18 (38%) patients in whom SEMS had been placed, died. The median survival in days from LTX was 1727 (range 98–3401) days. The lag period between SEMS insertion and death ranged from 6 to 1897 (median 157) days. The major cause of death was infection ($n = 14$), followed by malignancy ($n = 2$) and graft rejection ($n = 2$). Survival data indicate that the survival rates in LTX patients who underwent SEMS insertion at 1, 3 and 5 years were 75, 62.5 and 50%, respectively. The corresponding figures in LTX patients who did not require SEMS placement were 70.3, 66.2 and 62.5%, respectively (Fig. 3). No significant difference was noted in survival rates between LTX patients who underwent SEMS placement and those who did not ($P > 0.05$).

DISCUSSION

Airway complications in LTX recipients require treatment when there is a clinically important decline in lung function or when retention of secretions and recurrent infections occur [6–16]. Endobronchial correction of airway complications by laser and balloon dilatation, while permitting immediate relief of symptoms, is often besieged by recurrence, necessitating more definitive palliation with endobronchial stent placement. Sundset *et al.* [11] described in a recent report, excellent short- and long-term outcomes in 35 LTX patients in whom silicone stent had been placed. Most of the stents (25 of 35) could be easily removed after a median of 6 months. Dutau *et al.* [12] showed similar results in 17 LTX patients. While silicone stents are potentially retrievable, their narrow internal-to-external lumen diameter ratio, tendency to migrate and interference with mucociliary clearance are important considerations to be taken into account in LTX patients. In addition, silicone stent placement requires rigid bronchoscopy under general anaesthesia. Conversely, SEMS have a more favourable internal-to-external diameter profile and are technically easier to insert under conscious sedation by flexible bronchoscopy. Metallic stents frequently become epithelialized into the bronchial wall limiting the possibility of migration and allowing for optimal pulmonary hygiene. The fact that these stents are not easily removed [17], and their tendency to induce significant local granulation tissue formation in addition to the fact that

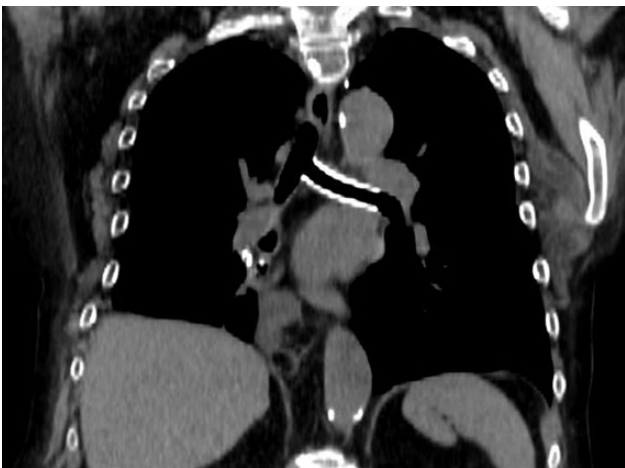


Figure 1: Coronal chest CT of a post-left LTX representative patient who developed severe bronchial stenosis 9 months following LTX that was relieved by self-expandable metallic stent placement in the left main bronchus.

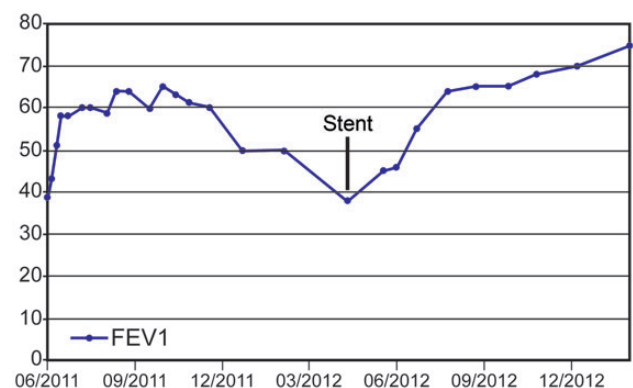


Figure 2: A plot of FEV₁ of the representative patient demonstrating severe drop in pulmonary function test secondary to bronchial stenosis that was relieved following self-expandable metallic stent placement.

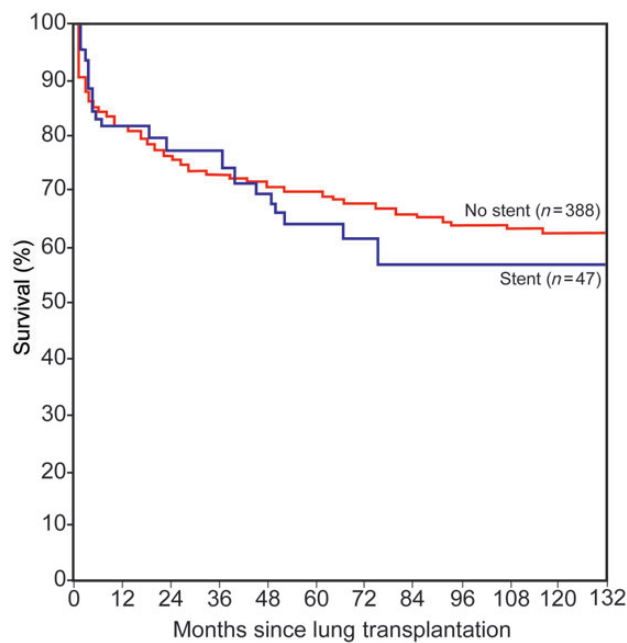


Figure 3: Kaplan-Meier plots of survival probability in LTX patients in whom self-expandable metallic stents were placed compared with patients without stents.

they potentially pose the risk of erosion and haemorrhage, has driven many transplantation centres to abandon their use.

The current cohort study provides novel information regarding longitudinal outcomes in lung allograft recipients in whom airway complications develop in the post-transplant period and required SEMS placement. According to our experience, placement of SEMS in LTX patients under conscious sedation can be accomplished with acceptable immediate complication rates. No life-threatening events occurred during or immediately after stent placement and no deaths were attributed to stent malfunction or malposition. The success rate of immediate dyspnoea relief is impressive (>90%). Whereas most of the patients needed bronchoscopic interventions to prevent stent stenosis due to granulation tissue formation, only 16% of patients needed stent removal that was easily accomplished using flexible bronchoscopy without the need for rigid bronchoscopy. The complete data of patients who needed SEMS removal have already been described by us [19]. Whereas previous reports have suggested that the use of SEMS in LTX patients should be restricted to a minimum due to excessive granulation tissue formation [18–20], we on the other hand [20] have noted that LTX patients tend to develop less granulation tissue than other patients in whom stents have been placed for the treatment of benign disorders. We speculate that the use of immunosuppressive agents in these patients may reduce the formation of granulation tissue formation compared with non-transplanted patients with stents. The long-term outcome of SEMS in LTX patients, according to our experience, was satisfactory. Long-term survival of LTX patients in whom SEMS was placed was similar to the survival of LTX subjects without stents. We believe that continuous stent maintenance by routine and scheduled follow-up bronchoscopy every 3–6 months is essential to maintain stent patency.

Our conclusions are in accordance with several previous investigators describing their experience in SEMS placement for LTX patients with airway disorders. Bolot *et al.* [21] described both immediate and durable improvement of symptoms in 18 patients

with 23 bronchial stenoses that were treated by Gianturco expandable stent. On the other hand, Tan *et al.* [22] reported disappointing results with AERO metallic covered stent in 6 patients in whom build-up of thick mucus was observed in all the stents remaining in the airway for longer than 1 week. Strictures recurred in all patients 1, 3 and 5 months after stent deployment. Anile *et al.* [23] reported successful relieve of airway stenoses with SEMS in 10 LTX patients, with low incidence of complications.

Only few reports to date provide long-term outcomes of SEMS in LTX patients. In the study by Chhajed *et al.* [24], 9 LTX patients underwent insertion of uncovered Ultraflex stents, with a mean follow-up of 263 ± 278 days. The mean improvement in FEV₁ after insertion of stents was ~ 600 ml. No patient with an Ultraflex stent developed mucus plugging or stenosis at stent extremity. In that report, no survival analysis was performed comparing LTX patients with and those without stents. In the second landmark study by Gottlieb *et al.* [17], 65 (9.2%) of 706 LTX patients, 111 (91% non-covered) bronchial SEMS were implanted a median of 133 days after LTX; follow-up was 777 (7–3.655) days. According to their experience, in SEMS patients, 5-year survival was significantly lower than in the total cohort (60 vs 76%; $P = 0.02$). Higher mortality in lung transplant recipients with SEMS may be explained by a higher risk of infection and lower functional reserve in case of complications. Although our study group is smaller than that reported by Gottlieb, it is one of the largest cohorts to date for whom we provide long-term follow-up data (54 months). According to our experience, we did not note a significant difference in survival between LTX patients with and those without SEMS. Our results are in accordance with those provided by Herrera *et al.* [2]. In their report, 18 LTX patients (13 single and 5 bilateral) required SEMS insertion. The mean increase in FEV₁ post-stenting was 87%. Two stent patients died from infectious complications. Six patients required further intervention. Long-term survival and FEV₁ did not differ from those of non-stented LTX patients. To note, the average follow-up in that cohort was significantly shorter than ours (24 months).

Biodegradable stents have been recently introduced into practice and may become the preferred modality for the treatment of LTX patients with airway complications in the future. Lischke *et al.* [25] conducted a small pilot study of 20 biodegradable stents that were implanted in 6 patients with post-transplant bronchial anastomotic stenoses. The stenosis was initially relieved in all cases; however, 4 patients needed multiple stenting for anastomotic restenosis, with a median time of 5 months to re-stenting. Surviving patients were in good clinical condition up to 4 years' follow-up (median 40 months) since first stenting. Until more data on biodegradable stents become available, according to our experience, SEMSs are a safe, effective and reliable alternative to silicone stents in patients with anastomotic stenosis after LTX.

Conflict of interest: none declared.

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