



# Bronchoscopic balloon dilatation in the management of bronchial stenosis following lung transplantation

J. De Gracia<sup>a,\*</sup>, M. Culebras<sup>a</sup>, A. Álvarez<sup>a,c</sup>, E. Catalán<sup>a</sup>, D. De la Rosa<sup>a</sup>, J. Maestre<sup>b</sup>, M. Canela<sup>b</sup>, A. Román<sup>a</sup>

<sup>a</sup>Department of Pneumology, Hospital Universitari Vall d' Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain

<sup>b</sup>Department of Thoracic Surgery, Hospital Universitari Vall d' Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain

<sup>c</sup>Predoctoral fellow, Department of Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain

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## KEYWORDS

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## Summary

**Background:** Bronchial stenosis (BS) is currently found in 7–15% of lung transplantation (LT) recipients. Current treatment strategies have included Nd:Yag laser, cryotherapy, bougie dilatation and stent placement. Bronchoscopic balloon dilatation has been used as alternative treatment in a few cases with controversial results. This is a study to prospectively assess the efficacy of bronchoscopic balloon dilatation as a first step in the management of post-LT BS.

**Methods:** From January 1995 to December 2002, bronchoscopic balloon dilatation was evaluated as first therapeutic option in all consecutive LT patients with BS. Symptoms, pulmonary function tests, airway diameter and use of other therapeutic techniques were evaluated.

**Results:** A total of 10 out of 284 anastomosed airways (3.5%) in 9 out of 152 LT patients were included in the study and follow-up lasted from 6 to 81 months. Dilatation of all but one BS met with initial success: increase of both luminal dimensions and forced vital capacity ( $P = 0.01$ ), and relief of symptoms. Bronchoscopic balloon dilatation long-term follow-up showed effective results in 5 out of 10 (50%) bronchial stenoses, after an average of 4 bronchoscopic balloon dilatation procedures (range 1–8). No severe complications were observed. Stent placement was required in the other 5 bronchial stenoses.

\*Corresponding author. Tel./fax: +34932746138.  
E-mail address: [jgracia@separ.es](mailto:jgracia@separ.es) (J. De Gracia).

*Conclusions:* Bronchoscopic balloon dilatation is a safe method that should be considered as first therapeutic treatment of post-LT BS. Its use avoids the need for stent placement in up to 50% of cases.

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## Introduction

Bronchial stenosis (BS) has been associated with illnesses of several etiologies.<sup>1</sup> Lung transplantation (LT), with an incidence of BS ranging from 7% to 15% of cases, is currently one of the most frequent causes.<sup>2</sup> Management of BS of any etiology, based on the application of cryotherapy, laser therapy, bougie dilatation during rigid bronchoscopy and stent placement, has displayed its efficacy depending on the site and features of the BS. Nevertheless, morbidity inherent or secondary to the procedure is frequent with these techniques,<sup>2-8</sup> especially secondary to stent placement, the most commonly used treatment, where complications have been observed in up to 75% of cases.<sup>7,8</sup> Bronchoscopic balloon dilatation (BBD) has recently been used as alternative treatment in retrospective studies,<sup>1-3,5,9,10</sup> four of which were performed only in LT recipients,<sup>2,3,5,10</sup> with low morbidity and limited efficacy. However, there are no studies evaluating efficacy of BBD as the first step in the management of these patients.

The aim of this study was to prospectively assess the efficacy of BBD using fiberoptic bronchoscopy (FOB) as definitive or contributing treatment of BS after LT.

## Patients and methods

From January 1995 to December 2002 all LT recipients transferred from the intensive care unit and diagnosed with BS by FOB were initially included in the study. BBD was indicated as the first therapeutic procedure in all patients with BS of over 50% of bronchus diameter confirmed by means of FOB. Patients with formal FOB contraindication or those not wishing to take part were ruled out from the study.

## Lung transplantation (LT)

LT, without revascularization procedures, were performed as described previously.<sup>11</sup> All patients were on the same immunosuppression protocol based on triple therapy with cyclosporine, azathioprine and corticosteroids. Acute rejection

was treated with pulse intravenous methylprednisolone for 3 days. Tacrolimus was included at the initial immunosuppression in some cases or as rescue therapy in patients with persistent or recurrent rejection. Occasionally, mycophenolate mofetil or methotrexate replaced azathioprine for the same indication.

All cytomegalovirus-seropositive recipients received ganciclovir prophylaxis for the first 45 days or in the case of seronegative recipients with a seropositive donor for 90 days. Similarly, all patients were treated with nebulized amphotericin B and oral cotrimoxazol prophylaxis three times a week for life.

## BS diagnosis

All patients had BS of over 50% of bronchus diameter confirmed by means of FOB (Fig. 1). At least one fiberoptic bronchoscopy was performed on all patients prior to discharge. Additional FOBs were indicated when respiratory symptoms were present and/or pulmonary function tests were suggestive of intrathoracic stenosis. Computed



Figure 1 Stenosis on intermedius bronchus.

tomography of the thorax was performed occasionally to evaluate the extent of the stenosis if necessary.

Mild anastomotic ischemia<sup>12</sup> was defined as moderate to severe airway erythema with or without mucosal friability or endobronchial plaques without thick white exudates. Moderate anastomotic ischemia was defined as thick white exudates or a black eschar covering less than 25% of the anastomotic circumference as viewed through the bronchoscope. And finally, severe anastomotic ischemia was defined as a black eschar covering more than 25%.

### Bronchoscopic balloon dilatation

FOB was always performed by the same operator as previously described.<sup>13</sup> In summary, 15 min prior to examination, 0.5 mg of atropine was injected subcutaneously. The upper airway was anesthetized with 5 mL of 1% lidocaine solution administered orally by nebulization, and additional small quantities of lidocaine were instilled through the bronchoscope as required to control coughing. FOB was carried out with fiberoptic bronchoscopes Pentax EB-1830 and FB-19 TX (Asahi Optical Co., Ltd. Tokyo, Japan), and Olympus BF 1T160 (Olympus America; Melville, NY). A variety of inflatable balloons was used with diameters of 5–14 mm and lengths from 2 to 4 cm (Balloon dilatation catheter; Medi-Tech<sup>®</sup>; Boston Scientific Corporation, Watertown, MA). Under bronchoscopic guidance, the balloon was placed across the stenosis using an adapted modification of Seldinger's technique.<sup>14</sup> Then, the balloon was gradually inflated with saline solution using the basic inflation syringe to maximum balloon pressure psi and was held for 30 s (Figs. 2 and 3). After deflation, if the airway was still narrow, and if the patient tolerated the dilatation with respect to oxygen saturation and hemodynamics, the procedure was repeated either with the same balloon or one with a larger diameter. Monitoring FOB was carried out 2 and 6 weeks post dilatation, and fresh dilatation interventions were indicated if stenosis recurred. After a follow-up of 6 months, BBD was considered effective only if freedom from BS was complete (complete resolution) or the remaining stenosis was under 50% of bronchus diameter as viewed through bronchoscope without stenosis-related symptoms (partial resolution). BBD was considered ineffective if other procedures were required because the patient remained symptomatic (cough, dyspnea) or a fall in pulmonary function tests was observed.



**Figure 2** Balloon placement across the intermedium bronchus stenosis.



**Figure 3** Immediate increase of luminal dimensions of the intermedium bronchus after bronchoscopic balloon dilatation.

### Stent placement

Ultraflex<sup>®</sup> stents (Boston Scientific; Watertown; MA, USA) were implanted as alternative therapy when BBD was ineffective. All procedures were performed by rigid bronchoscopy under general anaesthesia. In these cases, BBD was performed just prior to stent placement in those patients with previous immediate improvement.

## Clinical outcomes

Data in relation to: location of the stenosis (right main stem bronchus (RMSB), left main stem bronchus (LMSB), intermedius bronchus (IB) or bilateral); initial improvement in BS after BBD; evolution of respiratory function pre- and post dilatation (FEV<sub>1</sub>, FVC and FEV<sub>1</sub>/FVC); improvement of symptoms attributable to BS (cough, dyspnea); and procedure complications were collected.

## Statistical analysis

In most cases values are shown as means  $\pm$  standard deviation ( $X \pm SD$ ). The study of differences between qualitative variables was carried out using the  $\chi^2$  test and Fisher's exact test when necessary. The study of quantitative variables was established by means of Student's *t*-test for paired data.  $P < 0.05$  was considered significant. All data were analyzed using the statistical package SPSS, version 11.0, Chicago, IL.

This study was approved by the ethics committee of Vall d'Hebron Hospital, Barcelona, Spain.

## Results

Nine out of 152 patients (5.9%) with LT (20 single and 132 bilateral LT) were included (seven men, with average age of  $43.3 \pm 19$  years). In a total of 10 out of 284 anastomosed airways (3.5%) BS was detected (6 in IB, 3 in LMSB and 1 in RMSB) and followed through for an average of  $31.3 \pm 24.5$  months (range: 6–81). The rate of BS was similar between patients with single or bilateral LT (3/20 vs. 6/132 patients;  $P = 0.09$ ); but in anastomosed airways it was higher in single than bilateral LT (3/20 vs. 7/264 anastomosed airways;  $P = 0.02$ ). Average detection time for BS was  $137 \pm 73$  days (range: 64–274). Clinical features and follow-up data are presented in Table 1.

The first FOB was performed in all patients at  $15.8 \pm 12$  days (range: 3–38) following LT. Moderate-severe ischemia was observed in 7 of the 10 suture-lines (70%) which developed stenosis. Mild ischemia was noted in one suture-line and no ischemia in the other two suture-lines. The latter corresponded to a patient with bilateral BS who required placement of bilateral stent. In the 5 patients with bilateral LT and one BS, ischemia was observed in all the homolateral suture-lines of the bronchi which developed stenosis and in two of the contralateral suture-lines.

## Bronchial balloon dilatation (BBD)

In the 10 BS a total of 33 BBD were performed (mean  $3.67 \pm 2.6$ ; range 1–8). Immediate improvement in the stenosis, characterized by increased luminal dimensions, was obtained in 31 (94%). Two consecutive attempts at bronchial dilatation were inefficacious in a patient with LMSB stenosis who eventually required placement of an endobronchial stent (patient 5). The study of pulmonary function revealed a significant increase in absolute FVC values after BBD interventions ( $2.1 \pm 0.8$  L vs.  $2.4 \pm 1.0$  L,  $P = 0.01$ ). An increase in FEV<sub>1</sub> values was also observed but it was not significant ( $1.4 \pm 0.8$  L vs.  $1.5 \pm 0.9$  L,  $P = 0.237$ ). Improvement in cough and dyspnea was observed in 6 of the 7 patients with stenosis-related symptoms.

Long-term follow-up showed effective results in 5 out of 9 (55%) stenosed bronchi with immediate improvement in the stenosis with BBD. Complete resolution of BS occurred in 3 of these after an average of 2 BBD procedures (range 1–4). Partial resolution was obtained in the other 2 patients after an average of 7 BBD procedures (range 7–8) without associated symptoms after 24 and 75 months of follow-up. In the remaining four BS response to bronchial dilatation was ineffective after an average of 3 BBDs (range 2–4) (patients 2, 4 and 7).

The BBD procedures were always well-tolerated and with the exception of one slight hemorrhage just after dilatation no complications were observed secondary to the same.

## Stent placement

Stent placement was required in 5 BS (unilateral BS in 3 patients and bilateral BS in 1 patient). In a patient with LMSB stenosis (patient 5), it was indicated because BBD procedures were inefficacious in achieving an immediate improvement of BS. In the other 4 BS with initial efficacious BBD, stent placement was performed because BS re-appeared after a follow-up of 6 months. In the latter cases, BBD was indicated just prior to stent placement to make it easier.

## Comment

The findings of this study revealed a BS incidence of 3.5% of the bronchial anastomosis performed in LT recipients, and IB was the most frequent site (60% of cases). BBD proved to be a procedure with low morbidity. It resulted in temporary improvement in

**Table 1** Clinical features and follow-up of the patients.

Patient no.	Age (y)	Original disease	Transplant type	Site of ischemia (1st FOB)	Site of stenosis	Time from transplantation to diagnosis and BBD (days)	Number of dilatations	FVC <sub>pre</sub> /FVC <sub>post</sub> /FVC <sub>final</sub> (Litres)	Long-term resolution	Other treatments	Follow-up (months)*	Current status
1	62	COPD	BLT	Right suture-line	IB	114	8	3.2/4.1/4.3	Partial	No	24	Alive
2	50	BCh	BLT	Bilateral	IB	64	4	2.3/2.6/2.5	No	Stent	37	Dead (chronic rejection)
3	58	COPD	RSLT	Right suture-line	IB	86	7	1.9/2.1/2.3	Partial	No	75	Dead (chronic rejection)
4	57	COPD	BLT	Bilateral	IB	101	3	2.4/2.4/2.1	No	Stent	41	Dead (chronic rejection)
5	46	IPF	LSLT	Left suture-line	LMSB	165	2	1.9/2.0/1.8	No	Stent	31	Dead (chronic rejection)
6	59	IPF	LSLT	Left suture-line	LMSB	233	4	1.3/1.8/2.0	Complete	No	6	Dead (right lung cancer)
7	20	BCh	BLT	None	LMSB/IB	134	3	1.3/1.5/1.1	No	Stents	11	Dead (chronic rejection)
8	28	COPD	BLT	Right suture-line	IB	273	1	3.5/4.2/4.5	Complete	No	21	Dead (idiopathic interstitial pneumonia)
9	10	CF	BLT	Right suture-line	RMSB	70	1	1.0/1.4/1.4	Complete	No	81	Alive

COPD: chronic obstructive pulmonary disease; BCh: bronchiectasis; IPF: idiopathic pulmonary fibrosis; CF: cystic fibrosis; BLT: bilateral lung transplantation; RSLT: right single lung transplantation; LSLT: left single lung transplantation; IB: intermedium bronchus; LMSB: left main stem bronchus; RMSB: right main stem bronchus; FVC<sub>pre</sub>: FVC pre-dilatation; FVC<sub>post</sub>: FVC post-dilatation; FVC<sub>final</sub>: FVC 6 months after the last dilatation or FVC before the stent placement.

\*Since the diagnosis and first BBD procedure.

all cases except one and ensured maintenance of optimal airway luminal dimensions in the long term in half of them. It also proved useful in all cases in which BBD was required prior to insertion of a stent.

The pathogeny of BS secondary to LT has not been clarified yet, although ischemic damage (which affects the anastomosis area), rejection, and infection have been considered as individual and/or concomitant predisposing causes.<sup>15</sup> Furthermore, the frequency of stenosis far from the anastomosis (especially IB) is high and it leads us to assume that local aspects play a relevant role in its pathogeny. In this way, it is likely that deficient vascularisation in this region plays a major role.

The insertion of rigid or self-expandable stents<sup>7,8</sup> has been the most frequently used technique in the management of tracheobronchial stenosis of benign and malignant etiology. In LT patients, insertion of self-expandable stents (Wallstent<sup>®</sup> or Ultraflex<sup>®</sup>) allows immediate and long-term maintenance of optimal airway luminal dimensions in 80% and 45% of cases, respectively.<sup>16</sup> Nonetheless, several adverse effects such as infections and/or granulation tissue can be observed in over 60% of cases, similar to the other causes of stenosis.<sup>7,8</sup> Brachytherapy, after the failure of other techniques, has been proposed in few patients<sup>17</sup>, with poor results.

In benign tracheobronchial stenosis not due to LT, BBD has proved to be a straightforward technique. Morbidity is low and it is useful in achieving immediate and occasionally long-term increase of airway luminal dimensions.<sup>1</sup> Only a few studies have evaluated BBD in LT patients and they reported long-term variable efficacy (20–40%) and major conclusions are difficult to reach because of

differences in relation to methodology, indication, evaluation and follow-up.<sup>2,5,9,10</sup> In this way, the present study showed optimal long-term results in 50% of cases, which is the highest reported to date (Table 2). The results could be related to the following: in this study the use of BBD was the first therapeutic step in all cases; at least two BBD sessions were performed if necessary; and alternative therapy was considered only if residual stenosis was either over 50% of the bronchial diameter or under 50% with related symptoms.

In this report and in others, IB was the most frequent site of BS (60% of stenosis). In these cases, the use of stents is controversial because stent migration and right bronchial upper obstruction is common.<sup>8,17</sup> On the other hand, in our experience, repeated BBD sessions avoid the need for further treatment in 4 out of 6 cases during follow-up (range 21–75 months) of the patients.

Safety of BBD was outstanding as described above and prior to stent insertion it proved to be of great efficacy and without associated morbidity, and made stent placement easier. Its use must be first choice over bougie dilatation by rigid bronchoscope, a technique with greater associated morbidity. Moreover, although more patients with stenosis need stent placement, the complications associated with its use in LT recipients are well described<sup>2</sup>; therefore, it is desirable to limit its use whenever possible. The results of this study indicate that the use of BBD as first-line treatment reduces both stent placements and the utilisation of other techniques.

Our study has a certain bias. There is no control group and no alternative techniques were discussed due to the high ratio of complications secondary to

**Table 2** Comparison of results in treating bronchial stenosis secondary to lung transplantation in the present study and other studies.

Authors	Total number of BS	First-line treatment	Number of BS treated with BBD as first-line treatment	Number of stent placements/other procedures due to BBD failure	Number of BS treated with stent placement as first-line treatment
Sheski et al.	7	BBD	7 (100%)	3 (42.8%)/2 (28.6%)	0
Chhajed et al.	41	BBD or stent	31 (75.6%)	23 (74.2%)/0	10 (24.4%)
Colt et al.	6	BBD or stent	4 (40%)	3 (75%)/2 (50%)	2 (20%)*
Susanto et al.	12	BBD or stent	12 (100%)	7 (58.3%)/0	0
Carré et al.	12	BBD or stent	8 (66.7%)	4 (50%)/2 (25%)	4 (33.3%)
Ferretti et al.	10	BBD	10 (100%)	6 (60%)	0
Orons et al.	32	BBD or stent	5 (15.6%)	4 (80%)/0	27 (84.4%)
De Gracia et al.	10	BBD	10 (100%)	5 (50%)/0	0

BS: bronchial stenosis; BBD: bronchoscopic balloon dilatation.

\*This patient has been treated with laser too.

the latter and the limited number of patients. Furthermore, the absence of studies evaluating efficacy of BBD, a low morbidity procedure according to previous literature, as the first step in the management of BS secondary to LT, encourages us to design the study with BBD as elective technique in these patients. Consequently, it has not been possible to deal with some topics such as better survival times in patients treated only with BBD. Further studies with a greater number of cases are required to confirm this.

In conclusion, this study suggests that BBD is a procedure with low morbidity and of acceptable efficacy in the long term. It must be seriously considered as first choice procedure in BS of LT patients. Two or more sessions could be necessary until stable increase of airway luminal dimensions is obtained.

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