Endobronchial treatment of giant emphysematous bullae with one-way valves: a new approach for surgically unfit patients

Mario Santini*, Alfonso Fiorelli, Giovanni Vicidomini, Vincenzo Giuseppe Di Crescenzo, Gaetana Messina, Paolo Laperuta

Thoracic Surgery Unit, Second University of Naples, Naples, Italy

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Abstract

Objective: We aimed to evaluate the feasibility and short-term efficacy of endobronchial treatment with one-way valves for giant emphysematous bulla in surgically unfit patients. Methods: Nine consecutive patients with giant emphysematous bulla were enrolled in the last 3 years. Endobronchial valves were placed in the segmental bronchi to functionally isolate the airway that supplied the bulla, favouring the deflation of the bulla and its atelectasis. Mean value ± standard deviation of forced expiratory volume in 1 s (FEV1), preoperative forced vital capacity (FVC) and residual volume (RV) were: 1.0 ± 0.2 l (35 ± 9.9%), 1.5 ± 0.5 l (42 ± 12%) and 5.5 ± 0.7 l (231 ± 32%), respectively; and the values for diffusion capacity for carbon monoxide was 31 ± 4.6% and for the 6-min walk test (6MWT) was 156 ± 92 m; all patients required supplemental oxygen at rest. The St. George’s Respiratory Questionnaire (SGRQ) score was 85 ± 4.6. Results: At 24–48 h after the procedure, the mean value of FEV1 (from 35% to 47%, p < 0.01), FVC (from 42% to 52%, p < 0.01), diffusion lung capacity for carbon monoxide (DLCO) (from 31% to 33%, p < 0.05) and 6MWT (from 156 m to 281 m, p < 0.01) significantly improved with respect to baseline value. Conversely, mean value of total lung capacity (TLC) (from 157% to 123%, p < 0.01) RV (from 231% to 158%, p < 0.01) and SGRQ score (from 85 to 37, p < 0.01) was significantly lower than baseline data; these changes were preserved during the entire follow-up. Conclusion: Our preliminary data confirm the feasibility and the potential efficacy of this strategy with significantly immediate improvement of respiration and quality of life, which remains stable during 6 months of follow-up.

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1. Introduction

Giant emphysematous bulla (GEB) is defined as air-filled spaces, which occupies more than one-third of the hemithorax and develops in a lung destroyed by generalised emphysema [1]. In selected patients, surgery is the treatment of choice with improvement of lung function and quality of life [2,3]. A wide variety of surgical procedures have been proposed, such as local excision of the bullae, plication, stapler resection and lobectomy; videothoracoscopy is reported to be a good alternative to thoracotomy because of its lower invasiveness. However, there are still many cases considered to be high risk for surgery, despite surgical and anaesthesiological technical progress. In such patients, the optimal treatment is not still found despite a variety of less invasive strategy having been proposed [4–7]. The Zephyr endobronchial valves (EBVs; Zephyr; Pulmonx Inc., Redwood City, CA, USA) have recently emerged as a possible alternative to lung volume reduction surgery (LVRS) in selected patients, resulting in relief of dyspnoea and improved functional status [8–10].

Recently, we reported the first successful case in which the EBVs were used for the treatment of GEB [11]. Subsequently, we have described another case in which such device was successfully used to treat iatrogenic air leaks due to an inadvertent placement of chest drain in a GEB [12]. Based on these experiences, we prospectively followed all consecutive patients with GEB considered unfit for surgery and who thus underwent to bronchoscopic placement of EBV. The aim of the present study is to evaluate the feasibility of this technique by assessing the early and late modifications of pulmonary function data.

2. Materials and methods

2.1. Study design

This is a prospective, non-randomised, unicentre study to evaluate the safety and short-term efficacy of EBVs for the
treatment of GEB in patients unfit for surgery. EBVs were offered to such patients as a new investigational alternative to bullectomy. All patients enrolled in the study gave informed written consent, and the use of EBVs was approved by the Institutional Ethics Committee of the Second University of Naples.

2.2. Study population

Nine patients with GEB (nine men; median age, 64 years; range, 43–74 years) were the object of the study.

The clinical characteristics of study population are listed in Table 1. All patients experienced worsening dyspnoea, which required oxygen therapy. GEB was located in the upper left lobe in five cases, in the upper right lobe in two cases, in the lower right lobe in one case and one patient had bilateral GEBs in the right and left upper lobe, respectively.

Six patients (patients Number 2, Number 3, Number 6, Number 7, Number 8 and Number 9 of this series) had severe compromised pulmonary function, and thus were considered unsuitable for the surgical approach. Forced expiratory volume in 1 s (FEV1) was <30% in patients Number 6, Number 7 and Number 8; <35% in patient Number 9; and patients Number 2 and Number 3 had FEV1 <40%, but they presented severe hypercapnia with PaCO2 (partial pressure of carbon dioxide in the blood) >45 mm Hg. The forced vital capacity (FVC) was <50% in all six patients. Diffusion lung capacity for carbon monoxide (DLCO) was <30% in patients Number 6 and Number 7; <35% in patients Number 2 and Number 8; and <40% in patient Number 9.

In the remaining three patients (patients Number 1, Number 4 and Number 5 of this series), surgical resection was judged to be highly risky, given the significant co-morbidity due to their cardiac disease. The patients Number 1 and Number 5 presented pulmonary hypertension with pulmonary artery pressures of 45 and 46 mmHg, respectively; patient Number 4 had ventricular ejection fraction value of 15%.

Thus, all patients were reviewed for EBV treatment, according to standard acceptance criteria for bronchoscopic lung volume reduction (LVR) [8–10].

2.3. Clinical functional evaluation

Functional evaluation included spirometry, plethysmography, diffusing capacity (DLCO), exercise tolerance measured by 6-min walking testing (6MWT), PaO2 (partial pressure of oxygen in the blood) and PaCO2 (measured at rest while breathing room air). Particular attention was paid to the evidence of scissure in a target lobe site of the bulla on the basis of chest high-resolution computed tomography (HRCT) findings. Changes in patients’ quality of life were measured by the St. George’s Respiratory Questionnaire (SGRQ), which has a score ranging from 0 to 100, with a higher score indicating a worse quality of life [13]. The same examinations, performed before EBVs placement, were repeated at 24–48 h after the procedure, and at 1-, 3- and 6-month intervals. If clinically indicated, a review bronchoscopy was attempted.

2.4. Device description

The EBV is a bronchial implant incorporating a one-way silicone valve that is fashioned to drain air and secretions from the distal lung segment, while blocking entry of air. It is surrounded by a nitinol self-expandable mesh that anchors the valve within the bronchus. To provide a complete seal between the implant and the bronchial wall, the retainer is encased in a silicone membrane. In Italy, the EBV is provided in two sizes, each intended for a different range of target bronchial lumen diameters. The EBV 4.0 is designed for bronchial lumens with diameters of 4.0–7.0 mm, and the EBV 5.5 is designed for bronchial lumens with diameters of 5.5–8.5 mm.

2.5. Operative procedure

EBVs placement is similar to that described elsewhere [8–10]. It can be performed under general anaesthetics with endotracheal intubation, or generally under local anaesthetics. Briefly, the valve is inserted through the working channel of the bronroscope using a guided insertion device.
which is used to size the airway for proper placement. Valves were placed in lobar, segmental or subsegmental bronchi on the basis of individual anatomy to completely isolate the targeted lobe in correspondence to the bulla. When the EBV is delivered into the target bronchus, the retainer expands to contact the walls of the lumen.

2.6. Statistical analysis

All data were expressed as mean and standard deviation (SD). The preoperative data were used as the baseline and compared with postoperative data by paired Student’s t-test. A \( p \) value <0.05 was considered significant. MedCalc statistical software was used.

3. Results

3.1. Intra-operative results

The procedure was performed in two patients under general anaesthesia and in the rest of cases under local anaesthetics. There were 29 valves in place with a median of three valves (range, from two to six) per patient. The EBV 5.5 valves were used in 35% of the cases, and EBV 4.0 in 65%. Successful valve placement was accomplished in all patients. All patients tolerated the procedure very well; the median hospital stay was 3 days (range, from 2 to 5 days), and no patient need intensive care after the procedure.

3.2. Clinical follow-up

One patient (patient Number 1) (11%) developed ipsilateral pneumothorax 45 days post-procedure, which resolved with placement of drainage in Heimlich valve after 11 days. Two patients (patient Number 6 and patient Number 7) (22%) experienced haemoptysis at 3 and 4 months after the procedure, respectively. Review bronchoscopy showed granulation tissue around the valve, and in only one patient (patient Number 6) was valve removal required. At 6 months of follow-up, one patient (patient Number 8) presented a single pulmonary nodule within the lower right lobe not seen in the previous radiological controls (Fig. 2). The results of CT-guided needle-biopsy revealed it to be a bronchoalveolar carcinoma (T1N0M0). Thus, a wedge resection was performed via thoracotomy. This operation was possible because of the improved clinical respiratory status obtained after the EBV procedure. The patient is alive, and maintains the improvement of respiratory function.

3.3. Functional results

The results are shown in Table 2 and Fig. 1. At 24–48 h after the procedure, the mean value of FEV1 (from 35% to 47%, \( p < 0.01 \), FVC (from 42% to 52%, \( p < 0.01 \)), DLCO (from 31% to 33%, \( p < 0.05 \)) and 6MWT (from 156 m to 281 m, \( p < 0.01 \)) significantly improved with respect to baseline value, and remained constant throughout the entire follow-up period. Conversely, the mean value of total lung capacity (TLC) (from 157% to 123%, \( p < 0.01 \)) and of residual volume (RV) (from 231% to 158%, \( p < 0.01 \)) was significantly lower than baseline data; these changes were preserved during the entire follow-up period. \( \text{PaO}_2 \) and \( \text{PaCO}_2 \) were not significantly different before and after the procedure. However, during follow-up, one patient (patient Number 6) required less supplemental oxygen, whereas eight were able to stop it.

3.4. Radiological investigations

HRCT performed during the follow-up period showed complete atelectasis of the bulla in seven patients, and a residual small bulla in one patient (patient Number 3). Only one patient (patient Number 6) had no radiological improvement. Representative cases are reported in Figs. 2 and 3.

3.5. SGRQ score

There were significant changes in the SGRQ scores at all post-procedure time points compared with the procedure baseline. The mean score at 24–48 h (37 ± 12) was significantly lower than baseline data (85 ± 4.6) (\( p < 0.01 \)), and the changes were maintained during the entire follow-up (Fig. 4).

Table 2. Respiratory function test outcomes.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>24–48 h</th>
<th>1 month</th>
<th>3 months</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1 (l/s)</td>
<td>1.0 ± 0.2</td>
<td>1.4 ± 0.4*</td>
<td>1.5 ± 0.4*</td>
<td>1.5 ± 0.4*</td>
<td>1.8 ± 0.6*</td>
</tr>
<tr>
<td>FEV1 (%)</td>
<td>35 ± 9.9</td>
<td>47 ± 14*</td>
<td>52 ± 17*</td>
<td>53 ± 16*</td>
<td>54 ± 17*</td>
</tr>
<tr>
<td>FVC (%)</td>
<td>1.5 ± 0.3</td>
<td>1.9 ± 0.6*</td>
<td>2.2 ± 0.8*</td>
<td>2.2 ± 0.8*</td>
<td>2.3 ± 0.8*</td>
</tr>
<tr>
<td>TLC (l)</td>
<td>7.8 ± 0.4</td>
<td>6.6 ± 0.2*</td>
<td>6.6 ± 0.2*</td>
<td>6.7 ± 0.2*</td>
<td>6.6 ± 0.2*</td>
</tr>
<tr>
<td>TLC (%)</td>
<td>157 ± 12</td>
<td>123 ± 5*</td>
<td>122 ± 4*</td>
<td>122 ± 5*</td>
<td>121 ± 5*</td>
</tr>
<tr>
<td>RV (l)</td>
<td>5.5 ± 0.7</td>
<td>3.7 ± 1.2*</td>
<td>3.3 ± 0.7*</td>
<td>3.3 ± 0.7*</td>
<td>3.3 ± 0.7*</td>
</tr>
<tr>
<td>RV (%)</td>
<td>231 ± 32</td>
<td>158 ± 55*</td>
<td>142 ± 33*</td>
<td>158 ± 33*</td>
<td>137 ± 34*</td>
</tr>
<tr>
<td>DLCO (%)</td>
<td>31 ± 4.6</td>
<td>33 ± 4.8**</td>
<td>33 ± 4.6**</td>
<td>33 ± 4.6**</td>
<td>33 ± 4.6**</td>
</tr>
<tr>
<td>( \text{PaO}_2 )</td>
<td>57 ± 7.9</td>
<td>57 ± 5</td>
<td>58 ± 6.4</td>
<td>59 ± 5.7</td>
<td>60 ± 7.1</td>
</tr>
<tr>
<td>( \text{PaCO}_2 )</td>
<td>40 ± 4.6</td>
<td>37 ± 5.3</td>
<td>36 ± 4.4</td>
<td>36 ± 2.6</td>
<td>37 ± 1.8</td>
</tr>
<tr>
<td>6MWT (m)</td>
<td>156 ± 92</td>
<td>281 ± 87*</td>
<td>291 ± 93*</td>
<td>293 ± 98*</td>
<td>294 ± 102*</td>
</tr>
<tr>
<td>SGRQ</td>
<td>85 ± 4.6</td>
<td>37 ± 12*</td>
<td>33 ± 12*</td>
<td>31 ± 9*</td>
<td>34 ± 8*</td>
</tr>
</tbody>
</table>

Data are expressed as mean and standard deviation (SD). FVC: forced vital capacity; FEV1: forced expiratory volume in 1 s; TLC: total lung capacity; RV: residual volume; DLCO: diffusion capacity for carbon monoxide; 6MWT: 6-min walking testing; SGRQ: St. George’s Respiratory Questionnaire; \( *p < 0.01 \); \( **p < 0.05 \) (postoperative compared to baseline value).
4. Discussion

The current medical management of bullae is of limited scope, and surgery is the preferred option for GEB. Surgical resection has been found to improve symptoms, exercise tolerance and respiratory distress. Better results are anticipated for (1) younger patients with no co-morbidity, no weight loss and rapidly progressing dyspnoea; (2) normal or slightly decreased FVC; (3) FEV1 > 40% predicted; and (4) normal DLCO and arterial blood gas analysis. Conversely, Nakahara et al. [14] remark that functional improvement after bullectomy is unsatisfactory in patients with pre-operative FEV1 < 35% of predicted value, severe reduction of DLCO capacity, hypoxaemia and hypercapnia. The experience obtained in recent years with LVRS has, nevertheless, demonstrated that some improvement in pulmonary function may be observed after resection of pulmonary parenchyma in patients with advanced emphysema, in some cases by performing anatomical resections such as lobectomy [15–17]. However, it is difficult to assess the lower limit of tolerance for surgical resection in patients with severe emphysema because no single preoperative exam is considered to be an absolute predictor of post-operative morbidity and mortality. An FEV1 of 800 ml or less (30–35% of predicted), an FVC of 50% predicted or less as well as a room air partial pressure of CO2 > 45 mmHg and a partial pressure of O2 < 50 mmHg have all been historically associated with a marked increase in morbidity and mortality after a lung resection of any type [15,18].
On the basis of these considerations, six patients of our study group were judged unfit for bullectomy due to their severe compromised functional preoperative exams, as reported above. In the remaining three patients (patients Number 1, Number 4 and Number 5), operation was considered to be highly risky given the significant co-morbidity, as reported above.

Despite several alternative approaches having been proposed, unfortunately, there is still no one optimal method for treatment of GEB in surgically unfit patients.

In 1947, Monaldi introduced intracavitary drainage in a two-stage procedure for cavitary disease caused by tuberculosis [19]. An advanced one-stage procedure was reported in an article from Brompton Hospital [4]. This method was performed under thoracotomy with rib resection. In the Brompton Hospital series (31 patients), two patients (6.5%) died in the postoperative period because their respiratory function was too poor to allow even minimally invasive surgery. Theoretically, damage to the chest wall and post-thoracotomy pain had the potential to further worsen respiratory function in these critical patients. The same author accepts a preoperative FEV1 of 500 ml as a minimum prerequisite for such strategy.

Thus, Takizawa et al. [6] reported a CT-guided drainage of bulla as a less-invasive approach in patients with severe compromised respiratory function. This procedure does not require either muscle incision or rib resection, but it often ends in failure because of prolonged air leakage following drainage placement.

Recently, Bhattacharyya et al. [7] have reported a case of decompression of an emphysematous bulla through a transbronchial aspiration needle and instillation of some autologous blood into the bulla to induce its fibrosis, though the risk of complications, including pneumothorax and bronchopleural fistula, makes this procedure unsuitable for peripheral bullae.

Bronchoscopic placement of EBVs has been employed as a less invasive strategy to achieve LVR in selected patients [8–10]; they have then been applied successfully for occlusion of bronchopleural [20,21] and bronchocutaneous fistulas [22].

The rationale of EBV use as less invasive procedure for the treatment of GEB is based on the conventional view of the pathophysiology of bullous disease; bulla is defined as a localised area of parenchymal destruction supplied by airways that contain a valvular obstruction allowing gas to enter but not leave the cystic space. Continued alveolar destruction and the inflating effect of gas entering the space expand it, causing compression and collapse of the surrounding lung. This has been conceptually referred to as ‘intrapulmonary pneumothorax’ [23]. Thus, we postulate that the EBVs placement in all lobe segments in communication with the bulla may functionally isolate the airway that supplies the bulla. EBVs, working like a Heimlich valve, allow escape of air from the bulla at exhalation, but prevent air inflow at inhalation (Fig. 5(A)). This mechanism favours the deflation of the bulla and its atelectasis. The compressed lung re-expands with decrease of the dead space and improvement in the chest mechanics (Fig. 5(B)).

Theoretically, the endobronchial treatment of giant bulla might be viewed as a special case of bronchoscopic LVR. In both instances, the principle is to reduce lung volume by atelectasis of the worst-functioning lung tissue and to allow the re-expansion of compressed lung. The radiological evidence of scissure in a target lobe site of the GEB is one of the keys to obtain good results with this procedure. It avoids the risk of collateral ventilation through intersegmental connections (Kohn pores), which is one of the reasons for failures in the treatment of emphysema cases with EBVs. The Emphasys prosthesis is chosen for this issue because of its unique features; the one-way valve prevents the passage of air distally through the bulla, but allows the passage of secretions conversely to other prosthesis, stents, plugs and glues.
In this initial series of nine patients, we have observed a significant improvement in FEV1, in FVC and a significant reduction in RV and TLC. These results have been maintained during the follow-up course of 6 months. The improvement may be essentially explained with reduction of thoracic hyperinflation, re-expansion of adjacent compressed lung and improvement in respiratory muscle strength, chest wall mechanics and intrathoracic haemodynamics. Exercise capacity and DLCO were also improved and remained stable after 6 months of follow-up. The better efficiency in gas exchange may be due either to a reduction in dead-space ventilation or to net recruitment of functional alveolar capillary membrane.

Despite no significant changes of PaO2 and PaCO2 observed before and after procedure, the important result is that eight patients are able to stop oxygen therapy and one patient required less supplemental oxygen during the follow-up course. All patients had significant changes in the SGRQ scores at all post-procedure time points compared with the procedure baseline.

This technique is safe; few complications, including isplateral pneumothorax (1/9 patients, 11%) and haemophtysis (2/9 patients, 22%), were registered. However, pneumothorax and haemoptysis are well-known complications due to EBV placement, with an incidence ranging from 15% to 25% [8].

In only one patient are no-radiological changes seen after the procedure. This is patient who had a bilateral treatment, experienced massive haemoptysis 5 months later and required valves’ removal.

Despite that, the patient had a small increment in breathing capacity with improvement of symptoms, exercise tolerance and quality of life. These results, even in absence of collapse of bulla observed radiologically, could be explained by air flow being redirected to the relatively healthier portions of the lungs by EBVs, thus reducing physiological dead space and improving ventilation and perfusion mismatch. Actually, this patient is alive, and on the waiting list for lung transplantation. In such a case, EBV treatment may be advocated as a bridge to lung transplantation. When compared with other disorders (cystic fibrosis and idiopathic pulmonary fibrosis), the deterioration rate is slower and, with the new allocation score system [24], patients with generalised emphysema rarely gain priority on the waiting list until very late in the natural history of their disease. The placement of EBV may improve the quality of life and survival of these patients awaiting lung transplantation, as occurred in our case. Thus, in agreement with a recent article of Venuta et al. [25], this could be a useful indication to valve placement in the future and certainly requires further investigations.

Finally, in the era of cost containment, this procedure is not a cost-effectiveness approach. Actually, in Italy, the cost of the EBVs depends of their size; EBV 4.0 costs Euros 3,000, whereas the cost of EBV 5.5 is Euros 5,500. Considering that in our study group a median of three valves (two EBV 4.0 and one EBV 5.5) per patient are placed, the average cost per patient is estimated to be Euros 11 500.00. On the other hand, the EBV procedure is characterised by a shorter median hospital stay compared with that of surgical resection. The median hospital stay of our population is 3 days, and no patient needs intensive care after the procedure. Thus, a modest reduction in the intensive care unit and in hospital stay would justify the use of EBVs as a cost-effective procedure.

5. Conclusion

The use of EBV for the treatment of GEB appears to be highly promising. It is not a threat to bulllectomy, but an opportunity to benefit a wider spectrum of symptomatic patients who may not be candidates for surgical resection or who may be able to achieve palliation with less recovery and less risk. The technique proposed is unique as it only targets the bulla-affected lung, does not compromise existing lung function and allows the compressed but potentially functional lung parenchyma to contribute to post-procedure lung function. Our preliminary data remain encouraging.

The procedure provides immediate improvement of respiration, which is stable during 6-month follow-up and significantly improves quality of life. However, it needs larger series and long-term follow-up to be adequately validated.

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References