Comparing Clinical Outcomes in Upper versus Lower Lobe Endobronchial Valve Treatment in Severe Emphysema

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Key Words

Lung emphysema · Valve treatment · Heterogeneity · Outcome

Abstract

Background: Lung volume reduction surgery has been recommended for patients with upper lobe predominant emphysema and was associated with less favorable outcomes in patients with non-upper lobe predominant emphysema. The value of endobronchial valve (EBV) treatment in lower lobe predominant emphysema has not been studied. **Objectives:** To confirm the equivalence of upper and lower lobe valve treatments in patients with heterogeneous emphysema. **Methods:** A retrospective analysis from the Endobronchial Valve for Emphysema Palliation Trial (VENT), where patients with heterogeneous emphysema received Zephyr[®] EBV (Pulmonx Corp., Redwood City, Calif., USA) or medical treatment, was performed. Patients with low interlobar collateral ventilation and accurate placement of valves in the target lobes were identified. Safety and efficacy were compared between patients who underwent upper versus lower lobe treatment. **Results:** Of the 331 patients, 60 had low interlobar collateral ventilation and successful lobar exclusion (45 patients with upper lobe treatment and 15 patients with

lower lobe treatment). There was no difference in baseline characteristics between the groups except for a higher destruction score (70.3 vs. 60.7%; $p = 0.0010$) and a higher heterogeneity index (24 vs. 13%; $p = 0.0005$) for the upper lobe cohort. At 180 days, both groups had improved clinically. There were no significant differences in mean changes or responder rates of forced expiratory volume in 1 s (+23.8 vs. +22.9%), the St. Georges Respiratory Questionnaire (−6.50 vs. −7.53 points), the 6-min walk test (+24.1 vs. +44.0 m), target lobe volume reduction (−1,199 vs. −1,042 ml), or in the adverse event rate between both cohorts. **Conclusion:** Patients with lower and upper lobe predominant emphysema benefit equally from EBV therapy when interlobar collateral ventilation is low and lobar exclusion is achieved. Patients with lower lobe disease did not have increased adverse events compared to patients with upper lobe emphysema.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a common disease with increasing mortality and a high morbidity worldwide [1]. Chronic bronchitis, irreversible bronchoconstriction as well as emphysema destruction of

lung parenchyma associated with hyperinflation and impaired movement of the diaphragm lead to shortness of breath and limited exercise capacity with reduced quality of life. Early on in the course of the disease, an increase in the residual volume (RV) as an expression of progressive hyperinflation can be noted [2]. An increased respiratory rate during or after exertion leads to dyspnea due to the dynamic hyperinflation with an increase in the end-expiratory lung volume. Therefore, therapeutic interventions have to aim for a reduction in hyperinflation, with resulting improvement in forced expiratory volume in 1 s (FEV₁) and dyspnea [3].

Lung volume reduction surgery (LVRS) has been shown to effectively address these physiologic abnormalities, with resulting improvements in symptoms, lung function, and exercise tolerance in patients with advanced emphysema [4–6]. However, the largest study of LVRS, the National Emphysema Treatment Trial (NETT), suggested that patients with an upper lobe predominant pattern of disease benefit the most from LVRS. Furthermore, in NETT, a multivariate analysis indicated that a non-upper lobe predominant pattern of emphysema was independently predictive of 90-day mortality (odds ratio 2.99; $p = 0.009$) [7]. The observation that non-upper lobe predominant emphysema was associated with increased operative mortality and major cardiovascular morbidity as well as with decreased benefit directed the practice of LVRS to focus primarily on patients with heterogeneous disease located in the upper lobes.

Endobronchial lung volume reduction using one-way endobronchial valves (EBV) is designed to mimic the physiological effects of LVRS by unilaterally excluding the most diseased lobe of the lung from ventilation. Valves are placed in all the segmental bronchi (lobar exclusion), and the resulting deflation and absorption atelectasis reduce hyperinflation. However, lobar exclusion cannot be achieved in all patients due to the presence of extensive interlobar collaterals in the emphysematous lung [8, 9]. Nonetheless, studies have shown that patients with low interlobar collateral ventilation experience physiologic and functional benefits following EBV therapy similar to those seen following LVRS. In the largest study of valves, the Endobronchial Valve for Emphysema Palliation Trial (VENT), patients with complete interlobar fissures on baseline CT scans, which can be considered an approximate surrogate for low collateral ventilation, and successful lobar exclusion, had a 20.6% mean improvement in FEV₁ 6 months after treatment [8]. Although VENT and other studies have included both upper and lower lobe valve treatments, pub-

lications to date have not explored whether the safety and efficacy profiles of upper and lower lobe treatments are different, as they are with LVRS. In this retrospective analysis, we compared clinical outcomes and adverse events in the upper versus the lower lobe cohorts of VENT.

Patients and Methods

Study Design and Participants

Details of the trial design and study eligibility criteria for VENT have been reported previously [8–10]. In VENT, patients were screened using the modified NETT criteria for surgical candidacy. All patients underwent 6–8 weeks of a full pulmonary rehabilitation program. Patients who remained eligible for the study after undergoing the pulmonary rehabilitation program ($n = 492$) were randomly assigned 2:1 to receive EBV therapy using the Zephyr® EBV (Emphasys Medical, now Pulmonx Corp., Redwood City, Calif., USA) in the treatment group (331 patients) or standard medical care in the control group (161 patients). Patients in both study groups were followed up at 1, 3, 6, and 12 months. Subjects underwent bronchoscopic Zephyr® EBV implantation under the provisions of the protocol, which limited treatment to only one lobe, upper or lower, in one lung.

Quantitative CT Analysis

High-resolution CT (HRCT) images were obtained at baseline and 180 days and were analyzed by a radiology core laboratory. The core laboratory provided a report with the emphysema severity by lobe for inclusion eligibility, targeting and outcome measures at follow-up. A -910 Hounsfield unit threshold was used to define the percentage of voxels of the lobes in the emphysematous range and to subsequently define emphysema severity and heterogeneity. This percentage was then converted to a Likert scale, with a score of 1 for 1–25%, 2 for 26–50%, 3 for 51–75%, and 4 for 76–100%. Heterogeneity, defined as a 1-unit difference between the target and the non-target ipsilateral lobe, was required for inclusion. For targeting, a unilateral upper or lower lobar target was identified, with adequate disease severity to warrant total lobar occlusion and with heterogeneity or sufficiently preserved tissue in the adjacent ipsilateral lobe (the middle lobe was not considered as a target) [8].

Target lobe volume reduction (TLVR) was calculated by the radiology core laboratory, as follows: $TLVR = (\text{lobe volume at follow-up} - \text{lobe volume at baseline}) / \text{lobe volume at baseline}$.

Fissure Integrity and Lobar Isolation

All patients from VENT (US and European sites) who fulfilled the following criteria were included in the retrospective analysis: (1) complete fissure according to HRCT scan analysis at baseline, and (2) exhibiting lobar exclusion after EBV therapy at 6 months.

In this study, fissure integrity was assessed and scored on the thin-section, full-volume CT data acquired. Fissure integrity was scored on a scale of 0–4, as follows: 4, complete fissure; 3, >90% of fissure present; 2, 10–90% of fissure present; 1, <10% of fissure present, and 0, absent. A fissure integrity score of 3 or 4 was con-

Table 1. Baseline data of the patients with complete fissure and lobar exclusion grouped by lobe treated (i.e. upper vs. lower lobe)

	Upper lobe treatment	Lower lobe treatment	p value
Number of patients	45	15	
Males, %	60 (n = 27)	73 (n = 11)	0.3534
Age, years	62.2±7.6	64.9±8.2	0.2344
BMI	25.4±3.7	26.2±2.9	0.4381
Years as smoker	36.2±7.2	36.5±5.5	0.8952
Target lobe destruction score	70.3±9.3	60.7±9.3	0.0010
Heterogeneity, %	24±16	13±7	0.0005
FEV ₁ , l	0.90±0.32	0.86±0.25	0.6737
FEV ₁ , % pred.	29.8±7.7	29.1±7.9	0.4580
6MWT, m	349.0±90.3	366.4±77.2	0.5088
SGRQ, points	52.7±12.5 (n = 35)	53.9±11.2 (n = 12)	0.7683
TLV, ml	-1,227.0±767.8	-1,042.1±531.5	0.3945
RV, l	4.7±1.1	4.7±1.1	0.8542
TLC, l	7.5±1.3	7.4±1.3	0.9141

Data are given as the mean ± SD, unless otherwise specified. TLV = Target lobe volume.

sidered to indicate fissure completeness and therefore low interlobar collateral ventilation [11, 12]. Follow-up HRCT images were also reviewed to assess valve placement since incorrectly placed or an inadequate number of valves would prevent complete occlusion and hence lobar atelectasis. Visual assessment was performed by two thoracic radiologists to identify valve location and assess target lobe occlusion, which was defined as the presence of valves in each segment or proximal airway with complete occlusion of the target lobe airways.

Statistics

In this retrospective analysis, comparisons between upper and lower lobes for continuous outcomes were performed using a t test. Binary outcomes (such as responder rates or adverse events) were compared using either the χ^2 test or Fisher's exact test. Responders were defined according to established minimal clinically important differences, as follows: for FEV₁: $\geq +12\%$ (increase) [13]; for the 6-min walk test (6MWT): $\geq +26$ meters (increase) [14]; for quality of life measured by the St. Georges Respiratory Questionnaire (SGRQ): ≤ -4 points (reduction) [15]; for RV: ≤ -0.43 liters (reduction) [16], and for the dyspnea score measured by the modified Medical Research Council dyspnea scale: ≤ -1 point (reduction).

Results

Patient Population

Of 331 patients treated, 60 (18.1%) had complete fissures and successful lobar exclusion with complete follow-up data. Forty-five patients (75.0%) were treated in an upper lobe and 15 were treated in a lower lobe (25.0%). Baseline data for these subgroups are summarized in table 1.

There were no statistically significant differences between the two groups except for the destruction score and the heterogeneity index – the destruction score as well as the heterogeneity index were higher in the upper lobe treatment group than in the lower lobe treatment group (70.3 vs. 60.7%, $p = 0.0010$, and 24 vs. 13%, $p = 0.0005$).

Clinical Outcomes

At 180 days, both groups experienced improvements in lung function, exercise capacity, and quality of life. There were no statistically significant differences in the mean change in FEV₁, SGRQ, 6MWT, or TLVR in the upper versus lower lobe groups. However, there was a trend towards a higher reduction in RV (-0.40 ± 1.13 vs. -0.95 ± 0.90 liters; $p = 0.09$) and total lung capacity (TLC; -0.597 ± 0.652 vs. -0.142 ± 0.785 liters; $p = 0.05$) in the lower lobe group. The clinical outcomes in both groups are summarized in table 2.

The responder rates at 180 days, defined by minimal clinically important difference thresholds for each parameter are reported in table 3. There were no statistically significant differences between the upper and lower lobe groups even at the $p = 0.1$ level for FEV₁, SGRQ, 6MWT, the modified Medical Research Council dyspnea scale, or RV.

Safety Data

Major adverse events between the upper and lower lobe groups are compared in table 4. There were no statistically significant differences between the groups.

Discussion

EBV therapy and LVRS represent similar approaches to reducing lung hyperinflation; as such, the efficacy of both techniques further validates the critical role of hyperinflation in the physiology of advanced emphysema. VENT [8, 9] concluded that EBV therapy is associated with improvements in lung function, exercise capacity, and symptoms. Patients with low interlobar collateral ventilation and a complete occlusion of the targeted lobe will often benefit, and outcome results following significant TLVR are similar to those reported following LVRS [17]. Other EBV therapies that do not address reducing both hyperinflation and volume reduction of the most affected lung are not effective [18]. Therefore, only patients from VENT with both complete fissures and complete lobar occlusion (correct placement of the valves) were included in this retrospective analysis [19–21].

In NETT, non-upper lobe predominant emphysema was associated with decreased benefit and increased morbidity and mortality following LVRS. This may be caused by the fact that in this patient group, lower lobe emphysema and homogeneous emphysema cohorts were combined. Notably, in patients with homogeneous emphysema, the pathophysiology as well as the outcome seem to be different in comparison to patients with heterogeneous emphysema. Therefore, patients with a homogeneous emphysema distribution and very low FEV₁ (<20% pred.) have been identified to be high-risk patients for a surgical lung volume reduction [7]. A recent publication on the use of a polymer sealant (AeriSeal®, Aeris Therapeutics, Woburn, Mass., USA) for lung volume reduction in homogeneous patients noted decreased benefits in patients treated in the lower lobes and hypothesized that this was the result of relatively lower RV/TLC in the lower lobes compared to the upper lobes due to gravitational and anatomic effects [22]. However, this argument is not directly applicable to patients with heterogeneous disease.

The findings of NETT have not been universally replicated; in the study by Weder et al. [23], out of a cohort with 112 patients, 31 patients with a predominantly lower lobe disease distribution underwent surgical lung volume reduction. Though the improvement in FEV₁ was slightly lower in the lower lobe predominant cohort, the comparison of patients with upper lobe predominant disease to those with lower lobe predominant disease over a 5-year period did not show any statistically significant difference for multiple clinical endpoints. In another LVRS series of 21 alpha-1 antitrypsin deficiency patients,

Table 2. Clinical outcomes compared to baseline upper versus lower lobe treatments at 180 days

	Upper lobe treatment	Lower lobe treatment	p value
Number of patients	45	15	–
ΔFEV ₁ , l	+0.19±0.23	+0.17±0.17	0.71
ΔFEV ₁ , %	+23.8±26.4	+22.9±20.7	0.90
ΔFEV ₁ , % pred.	+6.6±7.7	+7.2±6.9	0.81
Δ6MWT, m	+24.06±67.7	+44.00±76.76	0.34
ΔSGRQ, points	–6.50±11.29	–7.53±17.55	0.82
ΔTLVR, ml	–1,199±779.7	–1,042±531.5	0.47
ΔRV, l	–0.40±1.13	–0.95±0.90	0.09
ΔTLC, l	–0.142±0.785	–0.597±0.652	0.05

Data are given as the mean ± SD, unless otherwise specified. TLV = Target lobe volume.

Table 3. Responder analysis: numbers and percentages of patients with minimal clinically important difference responses in the upper and lower lobes with complete fissures and lobar exclusion

	Upper lobe treatment		Lower lobe treatment		p value
	n/total	%	n/total	%	
FEV ₁	27/45	60	10/15	67	0.646
6MWT	24/45	53	8/15	53	>0.999
SGRQ	19/35	54	5/10	50	>0.999
RV	26/45	58	11/15	73	0.283
mMRC	16/33	48	5/12	42	0.685
TLVR	34/42	81	14/15	93	0.420

mMRC = Modified Medical Research Council dyspnea scale. Minimal clinically important difference threshold: FEV₁: ≥ +12% (increase); 6MWT: ≥ +26 m (increase); SGRQ: ≤ –4 points (reduction); RV: ≤ –0.43 liters (reduction), and modified Medical Research Council dyspnea scale: ≤ –1 point (reduction)

Table 4. Adverse event comparison between upper and lower lobe treatments

Event	Upper lobe treatment (n = 45)	Lower lobe treatment (n = 15)	p value (Fisher's exact test)
Death	2% (n = 1)	0	>0.05
Empyema	0	0	>0.05
Massive hemoptysis	0	0	>0.05
Pneumonia distal to valve	2% (n = 1)	0	>0.05
Air leak >7 days	9% (n = 4)	0	>0.05
Respiratory failure >24 h of ventilation support	2% (n = 1)	0	>0.05
Pneumothorax	18% (n = 8)	0	>0.05

Fig. 1. HRCT images of a patient with lower lobe predominant emphysema before (a) and after (b) EBV treatment in the left lower lobe. b Implanted EBV followed by atelectasis of the target lobe are visible (EBV; courtesy of Prof. C.P. Heussel, Thoraxklinik, University Heidelberg, Heidelberg, Germany).

10 of them had lower lobe predominant emphysema. Of the 4 patients with the longest-lasting treatment effect, 50% were in the lower lobe [24, 25]. Gelb et al. [26] also published a small LVRS case series of 6 patients with alpha-1 deficiency who showed postoperative improvements in lung function and dyspnea, though the improvements in FEV₁ were minimal. To date, multiple mechanisms have been hypothesized to explain why lower lobe predominant emphysema might be associated with less benefit and increased morbidity following LVRS, including limited access to surgical sites in the lower lobes and postoperative scarring in the peridiaphragmatic pleural space which could limit diaphragmatic excursion [27]. An additional point may be that after surgical shaving of the lower lobes, the remainder of the lung would not follow the given anatomy of the diaphragm and thoracic cavity. Since the above hypothesized mechanisms in lower lobe LVRS cases are not applicable to EBV therapy, there is no clear physiologic reason why patients with lower lobe predominant emphysema should respond differently from patients with upper lobe predominant emphysema (fig. 1, 2). However, the existing literature addressing this topic is limited. In a case series of 6 patients on the lung transplant list and treated with EBV therapy [28], 2 patients had upper lobe and 4 had lower lobe predominant patterns; there was no apparent difference between the groups, while the majority of the patients experienced a median reduction in target lobe volume of 724 ml associated with a median improvement in FEV₁ of 57%, an 11-point improvement in SGRQ, 110 percentage point reduction in RV% predicted, and a 71-meter increase in the 6MWT. Similarly, in another case series [29] of 15 alpha-1 antitrypsin deficiency patients with non-upper lobe targets treated with EBV therapy, 12 patients

Fig. 2. Corresponding bronchoscopic image with EBV in the left lower lobe bronchi.

were followed up for at least 1 year, and in these patients, FEV₁ increased by a mean of 54%.

The current report is the first systematic analysis comparing lower with upper lobe EBV therapy. The findings of this study confirm that patients with lower and upper lobe predominant emphysema benefit equally from EBV therapy when interlobar collateral ventilation is low and lobar exclusion is achieved. Improvements in lung function, 6MWT, and quality of life score did not differ sig-

nificantly in both groups. Although a nonsignificant trend for a higher reduction in RV and TLC was seen in the lower lobe group, it cannot be determined whether a lower lobe valve treatment is superior to an upper lobe treatment given the small sample size.

Furthermore, all major adverse events were seen in the upper lobe group, and no severe complications were seen in the lower lobe group. This fact may be caused by the small overall complication rate and the smaller number of patients in the lower lobe cohort. Furthermore the number of pneumothoraces – even though not statistically significant – appears to be higher in the upper lobe group. In a previous study [30], one third of the patients treated in the left upper lobe developed a pneumothorax, although it is known that a postinterventional pneumothorax is also possible after lower lobe occlusion [31]. Overall, patients with lower lobe predominant disease do not have an increased risk of major side effects. This is in contrast to the findings of NETT for LVRS. However, as

already stated, the hypothesized mechanisms which limit LVRS in the lower lobes do not apply to EBV therapy, since placement of valves in the lower lobes is no more difficult than in the upper lobes, and pleural scarring is not associated with the procedure.

The current study is limited by its retrospective design and relatively small sample size. Nevertheless, the findings are consistent with the limited existing literature and with the current understanding of the limitations of LVRS in lower lobe emphysema as described above. There were imbalances in some of the baseline characteristics between the lower and upper lobe groups; the mean destruction score and heterogeneity index were lower in the lower lobe group. However, these imbalances would tend to bias the lower lobe group towards smaller benefits since a higher destruction score and heterogeneity index are associated with larger responses to treatment. Therefore, the results support the conclusion that EBV therapy is at least as safe and effective in the lower lobes as in the upper lobes.

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