Endoscopic Lung Volume Reduction Using Endobronchial Valves in Patients with Severe Emphysema and Very Low FEV₁

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Key Words

Endoscopic lung volume reduction · Endobronchial valves · Severe emphysema

Abstract

Background: Patients with a forced expiratory volume in 1 s (FEV₁) below 20% of the predicted normal values (pred.) and either homogeneous emphysema or low diffusing capacity for carbon monoxide (DLCO) have a high risk for adverse events including death when undergoing surgical lung volume reduction. **Objectives:** We hypothesized that selected patients can benefit from endoscopic lung volume reduction (eLVR) despite a very low FEV₁. **Methods:** This study is a retrospective analysis of consecutive patients with severe airflow obstruction, an FEV₁ ≤20% of pred., and low DLCO who were treated by eLVR with endobronchial valves (EBV) between June 2012 and January 2015. Pre- and post-interventional lung function parameters, the 6-min walking test (6-MWT) distance, adverse events, and follow-up were

recorded. **Results:** In 20 patients, there was an overall improvement in lung function with an increase in FEV₁ (16.97–21.03% of pred.) and a decrease in residual volume (322–270% of pred.) and total lung capacity (144–129.06% of pred.). The 6-MWT distance improved (from 239 ± 77 to 267 ± 97 m overall, and from 184 ± 50 to 237 ± 101 m if patients developed an atelectasis of the target lobe). Pneumothorax occurred in 5 of the 20 patients (25%). 30-day mortality was 0%, and all patients survived to discharge. **Conclusions:** The patients benefitted moderately from EBV treatment despite an initially low FEV₁. Some patients improved remarkably. EBV treatment in patients with an FEV₁ ≤20% of pred. is generally feasible and safe. The greatest risk is pneumothorax with prolonged chest tube duration.

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Introduction

When patients with chronic obstructive pulmonary disease (COPD) develop severe emphysema associated with a reduced gas exchange area, pharmacologic therapy offers only few advantages. Hence, the therapy options are very limited for these patients. All therapeutic options except lung transplantation have a palliative character. Even if COPD patients are listed for lung transplantation, effective therapies are still needed to ameliorate their symptoms, as the waiting time on the transplant list is long and these patients rarely gain high priority on the waiting list.

Surgical lung volume reduction (sLVR) has been shown to improve lung function and quality of life in palliative care as well as in patients waiting for lung transplantation [1–4]. Nevertheless, the procedure has relevant risks, and not all patients are suitable to undergo sLVR. The National Emphysema Treatment Trial (NETT) showed high mortality rates within the first 30 days for patients with a low forced expiratory volume in 1 s (FEV_1) and either homogeneous emphysema or a very low diffusing capacity for carbon monoxide (DLCO) [4, 5]. Nevertheless, long-term follow-up of the high-risk patients of the NETT ultimately showed a benefit even in this subgroup [5].

Several studies have shown that endoscopic lung volume reduction (eLVR) with endobronchial valves (EBV) is an effective treatment for patients with emphysema. eLVR mimics basic principles of sLVR with a less invasive and fully reversible approach [6–8].

We hypothesized that eLVR provides a treatment option for patients meeting the NETT criterion for high risk; therefore we analyzed patients with a very low FEV_1 and very low DLCO undergoing eLVR in our institution.

Methods

Study Design and Participants

This study is a retrospective analysis of consecutive patients with severe airflow obstruction, an $FEV_1 \leq 20\%$ of predicted (pred.), and a low DLCO who were treated by eLVR between March 2012 and March 2015. From a computerized database, we retrieved all patients with severe emphysema and COPD GOLD stages III–IV referred to our department at the Saarland University Medical Center for eLVR. All patients were treated according to an institutional protocol to ensure a standardized procedure.

All patients had previously smoked cigarettes, but our protocol requested patients to have quit more than 3 months before the intervention. One prerequisite for treatment was established maximal pharmacological treatment (minimum: long-acting beta agonist, long-acting muscarinic antagonists, and inhaled corticosteroid). Pulmonary rehabilitation was not a prerequisite for treatment.

In this cohort, per protocol, every patient except 1 received 5 days of antibiotic treatment [sultamicillin (2×375 mg b.i.d.) and 50 mg prednisolone peri-interventionally]. We included all patients that had an $FEV_1 \leq 20\%$ of pred. and DLCO $< 20\%$ of pred. into this analysis. Homogeneous distribution of emphysema was not an exclusion criterion to treatment unless perfusion scintigraphy or SPECT/CT also showed a homogeneous distribution of perfusion, rendering the selection of a target lobe impossible. Before the procedure, all patients underwent functional testing including lung function, the 6-min walking test (6-MWT), DLCO (if possible), and blood gas analysis.

Acute exacerbation was excluded clinically and in laboratory analyses. Ventilation and perfusion scintigraphy (V/Q scanning) or perfusion scanning only and CT were assessed prior the intervention. Assessment of collateral ventilation (CV) was additionally performed to determine the target lobe. CV was measured using a catheter system (Chartis™; PulmonX, Redwood City, Calif., USA) during the same bronchoscopy procedure prior to the intervention.

Successful eLVR was defined as atelectasis on chest X-ray or CT. The clinical benefit from functional changes was defined by the minimal clinically important difference (MCID) between follow-up and baseline. The MCID for FEV_1 was reached at an increase of 100 ml [9], for residual volume (RV) it was reached with a 430-ml reduction [10], and for the 6-MWT distance if there was an increase of > 26 m [11].

Patients were discharged in clinically stable condition at least 4 days following eLVR. Follow-up for the current analysis was scheduled 4–6 weeks after the procedure. The study was approved by the institutional review board (Ärztchamber des Saarlandes; No. 35/15). The necessity for informed consent was waived by the institutional review board due to the retrospective nature of the study.

Pulmonary Function Tests and 6-MWT

Pulmonary function tests were performed with a Jaeger Master-Screen Body System (CareFusion, Rolle, Switzerland); static lung volumes were determined by whole-body plethysmography. DLCO was measured by using the single-breath technique. All measurements were performed according to the American Thoracic Society (ATS) and the European Respiratory Society (ERS) guidelines [12–14].

The 6-MWT was measured in all patients on a 70-meter floor after providing standard instructions [15]. The patients were not encouraged during the test [16]. All patients were familiar with the 6-MWT before study entry. During the 6-MWT, supplemental oxygen was administered through a nasal cannula as needed to maintain the arterial oxygen saturation at $\geq 90\%$. These standards were kept before and after eLVR.

Procedure

Bronchoscopy and periprocedural preparations were performed according to our internal standard. All interventions were performed under total intravenous anesthesia. The patients were intubated and mechanically ventilated.

Valves (Zephyr EBV; PulmonX) were placed unilaterally in lobar, segmental, or subsegmental bronchi based on the individual anatomic conditions with the intention of completely isolating the target lobe. Valves are available in two sizes, spanning airway diameters of 4.0–7.0 and 5.5–8.5 mm. All patients underwent a chest X-ray 1 h after the procedure (or earlier if symptoms occurred) to exclude a pneumothorax. In analogy to a surgical approach, 13/20 patients (65%) were treated bilaterally, but staged (2 patients re-

Table 1. Baseline characteristics of the patients undergoing eLVR

Clinical presentation	
Age, years	57.21±6.22
Male	11/20 (55)
BMI	21.57±4.1
BODE index	7±1.41
Listed for LTX at time of intervention	5/20 (25)
Currently listed for LTX	8/20 (40)
Mean LAS	34.98±5.45 (25.09–46.30)
Arterial blood gas	
PaO ₂ <55 mm Hg and/or LTOT	19/20 (95)
PaCO ₂ >50 mm Hg	8/20 (40)
6-MWT distance ^a , m	249±102 (86–448)
DLCO <20% of pred. ^b	17/17 (100)
<i>Baseline lung function</i>	
FEV ₁	
Liters	0.50±0.13 (0.30–0.74)
Percent of pred.	16.99±2.61 (11–20)
Vital capacity	
Liters	1.80±0.77 (0.61–3.61)
Percent of pred.	47.36±12.98 (27–73)
RV	
Liters	6.79±1.50 (3.61–9.63)
Percent of pred.	322.51±75.42 (232–577)
TLC	
Liters	8.55±1.92 (4.22–12.20)
Percent of pred.	144.53±25.33 (110–213)
RV/TLC, %	78.29±6.03 (63–85)

Values are presented as n (%) or means ± SD (range). BMI = Body mass index; BODE = body mass index, airflow obstruction, dyspnea and exercise capacity [29]; LTX = lung transplantation; LAS = lung allocation score; LTOT = long-term oxygen therapy; PaO₂ = partial pressure of oxygen; PaCO₂ = partial pressure of carbon dioxide. ^a n = 17. ^b Diffusing capacity was available in 17 cases; in 3 patients, vital capacity was too low to exactly determine DLCO.

ceived LVR coils due to CV on one side and EBV on the other side). We included only the first EBV procedure in this analysis to avoid interdependence. All reported outcome data were taken prior to a possible second treatment.

Statistical Analysis

Statistical analysis was performed using SPSS version 21 (SPSS Inc., Chicago, Ill., USA). Data were analyzed using Wilcoxon's signed-rank test. Results were considered statistically significant for p values <0.05.

Results

Baseline Characteristics of the Study Population

Twenty emphysema patients who fulfilled the above-mentioned criteria underwent eLVR at our center. Their baseline characteristics are shown in table 1. The mean

FEV₁ was 0.50 ± 0.13 (0.30–0.74) liters, equaling 16.99 ± 2.6% of pred. at a total lung capacity (TLC) of 8.55 ± 1.92 (4.22–12.20) liters and 144.50 ± 25.33% of pred. RV was 6.80 ± 1.50 (3.61–9.63) liters, equaling 322.50 ± 75.40% of pred.; thus the RV/TLC ratio was increased to 78.29 ± 6.03% of pred. The BODE index was 7.0 ± 1.41. The majority of the patients (19/20; 95%) had low partial pressure of oxygen; 8 patients (40%) showed chronic respiratory failure with elevated partial pressure of carbon dioxide. The diffusing capacity was available in 17 cases (85%), and the DLCO was <20% pred. in all of them. In 3 patients, vital capacity was too low to exactly determine the DLCO. Presumably, their DLCO was <20% pred. as well.

At the time of the intervention, 5 patients (25%) were listed for lung transplantation. At the present time, 8 patients (40%) in this group are listed, and 1 patient has undergone lung transplantation.

Table 2. Collateral ventilation, treated lobe, and radiologic response

	Patients	PTX	Atelectasis	Atelectasis with or without PTX
Collateral ventilation according to Chartis				
Positive	1/20 (5)	0/1 (0)	0/1 (0)	0/2 (0)
Negative	17/20 (85)	5/17 (29.4)	6/17 (35)	11/17 (55)
Likely negative	2/20 (10)	0/2 (0)	0/2 (0)	0/2 (0)
Target lobe				
LUL	7/20 (35)	3/7 (42.9)	2/7 (28.6)	5/7 (71.4)
LLL	5/20 (25)	2/5 (40)	1/5 (20)	3/5 (60)
RUL	5/20 (25)	0/5 (0)	3/5 (60)	3/5 (60)
RLL	3/20 (15)	0/3 (0)	0/3 (0)	0/3 (0)
Emphysema distribution ^a				
Homogeneous	13/20 (45)	3/9 (33.3)	1/9 (16.7)	4/9 (44.4)
Heterogeneous	7/20 (55)	2/11 (18.2)	5/11 (45.5)	7/11 (63.6)

Values are presented as n (%). Radiologic response is defined as presence of atelectasis in the target lobe or postinterventional pneumothorax. PTX = Pneumothorax; LUL = left upper lobe; LLL = left lower lobe; RUL = right upper lobe; RLL = right lower lobe. ^a Emphysema distribution is according to interventional pneumologists.

Emphysema Distribution and CV

The preinterventional CT scan showed a homogeneous emphysema distribution in 9 cases (45%). All patients had heterogeneous perfusion as shown by the V/Q scan or SPECT/CT.

CV could be excluded by Chartis™ measurement in 17 patients (85%). In 2 cases (10%), our measurement yielded no definitive result, as airways had collapsed, and in 1 case we found evidence for minimal residual CV. The results of the Chartis™ measurements are shown in table 2.

Interventional Treatment and Adverse Events

The most frequently treated lobe was the left upper lobe (7/20; 35%), followed by the left lower and the right upper lobe (5/20; 25%). A pneumothorax occurred in 5 cases (25%). All pneumothoraces were located on the left side. Three of the 5 occurred following left upper lobe treatment.

The patients who developed a pneumothorax showed mixed clinical courses. The majority had a prolonged air leak of a mean duration of 21.8 ± 12.4 days. Pneumothoraces occurred within 24 h following the intervention in all cases.

We had to remove the valves in 2 cases due to persisting air leaks after 6 and 35 days, respectively. The valve extraction after 6 days was due to a major air leak. After valve removal, the patient was on a chest tube for another 27 days. These 2 patients showed a clinical deterioration with both a decline in their lung function and the 6-MWT distance. The other 3 patients benefitted from EBV treat-

Table 3. Adverse events

Pneumothorax	5/20 (25)
Pneumothorax ≥ 14 days	3/5 (60)
Duration of chest tube, days	22.2 ± 12.42 (10–41)
Additional chest tube	2/5 (40)
Repeated pneumothorax	1/5 (20)
Valves removed	2/20 (10)
Mild exacerbation after bronchoscopy	3/20 (15)
Pneumonia	0/20 (0)
Valve migration	0/20 (0)

Values are presented as n (%) or mean $\pm$ SD (range).

ment despite drainage times between 8 and 14 days. One patient developed a pneumothorax ipsilateral to the treated lobe 768 days after the procedure. This event was not rated as a procedure-associated pneumothorax. Six patients (30%) developed an atelectasis without occurrence of a pneumothorax (table 3).

No pneumonia occurred after EBV placement. No valve migration or loss of valves occurred. All patients survived the treatment; the 30-day mortality was 0%.

Functional Results of Interventional Treatment

There was an overall improvement in lung function with an increase in FEV₁ and a decrease in RV and TLC. Subsequently, there was a reduction of the RV/TLC ratio, as shown in table 4.

Table 4. Functional characteristics of the patients prior to and after eLVR

	Baseline	Follow-up	Δ	p	Responder rate
FEV ₁ , l	0.50±0.13; 0.51	0.61±0.15; 0.61	+0.11±0.15; +0.04	<i>0.001</i>	5/20 (25.0)
FEV ₁ , %	16.99±2.61; 18.00	21.05±6.71; 19.35	+4.06±6.94; +1.25	<i>0.001</i>	–
VC, l	1.80±0.77; 1.69	1.89±0.47; 1.94	+0.10±0.64; +0.17	0.227	–
VC, %	47.36±12.98; 46.75	52.35±13.31; 49.60	+5.00±16.73; +6.50	0.126	–
RV, l	6.79±1.50; 6.55	5.70±1.6; 5.80	–1.10±1.64; –0.59	<i>0.005</i>	11/19 (57.9)
RV, %	322.51±75.42; 318.85	270.53±47.82; 264.50	–49.71±98.83; –24.70	<i>0.033</i>	–
TLC, l	8.55±1.92; 8.63	7.85±2.38; 7.78	–0.73±1.68; –0.46	0.070	–
TLC, %	144.53±25.33; 140.05	129.07±19.20; 124.00	–14.85±30.76; –6.10	0.059	–
RV/TLC	78.29±6.03; 79.46	75.86±0.74; 75.70	–2.23±9.57; –0.22	0.376	–
6-MWT dist., m	239.65±76.73; 240.00	267.45±98.35; 275.00	+50±0.51; +50.00	0.191	10/20 (50.0)

Values are presented as ‘means ± SD; medians’ or n (%). n = 20 patients, time to follow-up was 4–6 weeks. In 1 patient, whole-body plethysmography could not be performed for follow-up. Δ Differences between before and after treatment. Responder rate: the number of patients for whom the change met or exceeded the MCID for FEV₁ (increase of >100 ml), RV (decrease of >430 ml), and 6-MWT distance (increase of >26 m). p ≤ 0.05 for Wilcoxon’s signed-rank test was considered statistically significant (in italics). VC = Vital capacity; dist. = distance.

Table 5. Functional characteristics of the patients prior to and after eLVR according to the different emphysema distribution and development of atelectasis

	Homogeneous Δ (n = 9)	Homogeneous responder rate	Heterogeneous Δ (n = 11)	Heterogeneous responder rate	Atelectasis Δ (n = 9)	Atelectasis responder rate
FEV ₁ , l	+0.07±0.08; +0.06	1/9 (11.1)	+0.15±0.19; +0.03	4/11 (36.4)	+0.14±20; 0.03	3/9 (33.3)
FEV ₁ , %	+1.71±4.00; +1.00	–	+5.98±8.34; +1.10	–	+5.80±8.62; 1.40	–
VC, l	–0.08±0.78; +0.19	–	+0.24±0.49; +0.14	–	+0.23±0.81; 0.39	–
VC, %	+0.99±18.87; +8.5	–	+8.27±14.86; +4.50	–	+10.24±20.83; 15.40	–
RV, l	–0.71±2.07; –0.04	4/9 (44.4)	–1.45±1.12; –1.60	7/10 (70)	–1.46±2.14; –1.96	5/9 (55.6)
RV, %	–28.08±130.40; –1.00	–	–69.18±59.41; –55.50	–	–77.09±124.65; –58.80	–
TLC, l	–0.57±1.82; –0.27	–	–0.87±1.61; –1.13	–	–1.22±1.71; –0.94	–
TLC, %	–11.07±36.20; –5.70	–	–18.26±26.47; –18.35	–	–23.60±35.51; 14.40	–
RV/TLC	+2.10±9.50; +2.93	–	–6.11±8.21; –6.27	–	–5.40±11.89; –7.95	–
6-MWT dist., m	+31.67±63.59; +35	5/9 (55.6)	+24.64±81.02; +5.00	4/11 (45.5)	+53±78.58; +35	5/9 (55.6)

Values are presented as ‘means ± SD; medians’ or n (%). In the group of patients with atelectasis, 2 patients were excluded, as valves had to be removed. In 1 patient, whole-body plethysmography could not be performed for follow-up. Δ Differences between before and after treatment. Responder rate: the number of patients for whom the change met or exceeded the MCID for FEV₁ (increase of >100 ml), RV (decrease of >430 ml), and 6-MWT distance (increase of >26 m). dist. = Distance.

Eleven of 19 patients (55%) developed an atelectasis of the target lobe. The MCID for FEV₁ (l) was reached in 5/20 cases (25%), for RV (l) in 11/19 cases (57.9%), and for 6-MWT distance in 10/20 cases (50%).

Next, we analyzed the functional response differentially regarding emphysema distribution. Patients with homogeneous emphysema distribution showed a weaker lung functional response to treatment; the MCID for FEV₁ (l) was reached in 11.1%, and only 44.4% of the pa-

tients showed a relevant reduction in RV (l). Greater improvement was seen in the patients with heterogeneous emphysema distribution. These patients benefitted in terms of FEV₁ (l) in 36.4% and in terms of RV (l) in 70% of the cases. Patients with atelectasis were comparable to patients with heterogeneous emphysema distribution regarding their lung functional response (table 5). In the 6-MWT, all patients improved across the different groups with a relevant overall improvement in 50% of the cases and in 55.6, 45.5, and 55.6%, respectively, within the three subgroups (tables 4, 5).

Discussion

This retrospective analysis of 20 carefully selected patients with high-risk criteria according to the NETT [17] showed that eLVR improves lung function and exercise capacity in individual patients. The main complications were pneumothoraces. All patients survived to discharge. Short-term complications were of lesser importance compared to the reported 16% 30-day mortality among high-risk patients following sLVR [5].

The only nonpalliative treatment option for end-stage COPD patients is lung transplantation. Most patients do not qualify for transplantation, and the demand for organs exceeds their availability by far. As these patients usually remain symptomatic despite optimal conservative treatment, there is a great need for therapies that actually improve the burden of symptoms [18].

Hyperinflation and expiratory airflow limitation play a key role in dyspnea and functional limitations [19]. Both surgical and endoscopic techniques target and improve these parameters [2, 4, 6–8]. The NETT, while showing the efficacy of the method, might have led to an underuse of sLVR due to surgical morbidity and mortality [4, 17]. Hence, there is a quest for minimally invasive techniques that can produce significant functional, quality-of-life, and survival benefits for patients with severe COPD. There might be a trend towards an overuse of endoscopic methods, and clearly defined strategies for patient selection are still lacking.

The most hazardous complication in the first randomized trial of eLVR using EBV – besides increased rates of exacerbations, hemoptysis, and pneumonia – was the development of a pneumothorax (at a rate of 4.2%) [6]. This proportionally low rate of pneumothoraces is caused by a low rate of complete fissures, leading to CV and incomplete lobar occlusion [20]. Due to an improved patient selection in consideration of catheter-based CV assess-

ment [21–24] and CT-based analysis [24, 25], the rate of pneumothoraces increases up to 25–30%, as in the current analysis.

Pneumothorax following eLVR is a potentially lethal complication in these frail patients. Prolonged air leaks are reported in 68% of cases [23]. The current recommendation to remove valves stepwise following a chest tube duration longer than 9 days may dilute the success of eLVR in this group of patients [26]. The majority of patients in our cohort had an air leak for more than 14 days. We had to remove the valves in 2 cases due to persisting air leaks, but all patients could be managed conservatively by chest tube.

Our patients showed a moderate improvement after eLVR. Despite a mean volume reduction of –1.1 liters RV and a responder rate of 57.9% regarding RV (l), the MCID for FEV₁ (l) was only reached for 25% of the patients, and only 50% improved their 6-MWT distance above the MCID.

The subgroups with heterogeneous emphysema distribution and atelectasis presented higher response rates: up to 33.3–36% regarding FEV₁ (l) and 55.6–70% regarding RV (l). The mean RV reduction in heterogeneous and atelectasis patients was 1.46 and 1.45 liters, respectively. Nevertheless, the 6-MWT response rate within these subgroups was still only 45 and 55.6%, respectively.

If we compare our cohort to a very similar cohort undergoing sLVR fulfilling high-risk criteria according to the NETT, it has to be stated that the lung functional and exercise results exceed the currently reported interventional results by far [27]. This is true despite the fact that the patients with a heterogeneous emphysema distribution in our group had a much greater volume reduction after EBV treatment than reported previously [6, 25, 28]. Thus, surgery for LVR may have advantageous effects also in these high-risk patients, at least if provided at an experienced center. Our study is in line with the recently published, prospective, randomized controlled trial STELVIO by Klooster et al. [8] that showed very similar results regarding the changes in lung function. However, this trial found a better functional improvement in the treated patients. Of note, as in this trial, the majority of our patients were CV negative (19 of 20 treated patients). One reason why our patients failed to transfer lung functional changes into functional improvement might be due to the short interval between intervention and follow-up of 4–6 weeks compared to 6 months in the STELVIO trial.

According to a BODE index of 7, these patients had – apart from severe functional restrictions – also a poor

prognosis, with a predicted mortality rate of up to 80% at 52 months [29]. The BODE index is widely used as a surrogate for survival in COPD patients, especially when only a short-term follow-up is available. A recent report indicates better survival among patients with atelectasis after EBV treatment [30]; it is unclear if this holds true for this cohort, though.

Our study has important limitations that need to be addressed. Despite the fact that treatment was performed according to standardized operating procedures with a written policy, it is nevertheless a retrospective and post hoc analysis. Additionally, we did not perform a thorough analysis of the patients' quality of life. One reason why this might be important is that there might also be a placebo effect, and there was no control group. This would have been interesting additional information; however, the data finally were not available for most patients.

In conclusion, eLVR in patients with a low FEV₁ and DLCO is generally feasible and safe. A pneumothorax pos-

es the greatest risk for these patients. Compared to a previously published surgical cohort study, our results were not as good as those achieved with the surgical approach. Patients who qualify for the principle of reducing hyperinflation in COPD should be discussed in an interdisciplinary team on the basis of all information available at the centers capable of both surgical and endoscopic approaches.

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