Consolidating Lung Volume Reduction Surgery After Endoscopic Lung Volume Reduction Failure

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Background. **Bronchoscopic valve placement constitutes an effective endoscopic lung volume reduction (ELVR) therapy in patients with severe emphysema and low collateral ventilation. After the most destroyed lobe is occluded with valves, significant target lobe volume reduction leads to improvements in lung function, exercise capacity, and quality of life. The effects are not consistent in some patients, leading to long-term therapy failure. We hypothesized that surgical lung volume reduction (LVRS) would reestablish ELVR short-term clinical improvements after ELVR long-term failure.**

Methods. **This retrospective single-center analysis included all patients who underwent consolidating LVRS by lobectomy after long-term failure of valve therapy between 2010 and 2015. Changes in forced expiratory volume in 1 second, residual volume, 6-minute walking distance, and Modified Medical Research Council dyspnea score 90 days after ELVR and LVRS were analyzed, and the outcomes of both procedures were compared.**

Results. **LVRS was performed in 20 patients after ELVR failure. A lower lobectomy was performed in 90%. The 30-day mortality of the cohort was 0% and 90-day mortality was 5% (1 of 20). The remaining 19 patients showed a significant increase in forced expiratory volume in 1 second (+27.5% ± 19.4%) and a reduction in residual volume (−21.0% ± 17.4%) and total lung capacity (−11.1% ± 11.1%). This resulted in significant improvements in exercise tolerance (6-minute walking distance: +56 ± 60 m) and relief of dyspnea (ΔModified Medical Research Council: −1.8 ± 1.4 points.).**

Conclusions. **Consolidating LVRS by lobectomy after failure of a previously successful ELVR is feasible and results in significant symptom relief and improvement of lung function.**

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Chronic obstructive pulmonary disease (COPD) is a progressive, life-threatening syndrome characterized by chronic bronchitis and airflow obstruction, leading to hyperinflation and emphysematous lung destruction. Lung volume reduction surgery (LVRS) effectively reduces hyperinflation by resecting destroyed emphysematous lung tissue. The immediate improvement in respiratory mechanics and ventilation leads to improved lung function, exercise tolerance, dyspnea relief, and long-term survival in carefully selected patients.[1-3] Although LVRS has been proven to be an effective treatment modality in appropriately selected patients, the procedure is relatively underused because of concerns about associated morbidity and narrow patient eligibility criteria.[4]

Endoscopic lung volume reduction (ELVR) aims at overcoming these limitations by providing the benefits seen with LVRS but reducing procedure-associated morbidity and mortality. Blocking methods, such as valve implantation, and nonblocking methods, such as

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coil implants, are used to induce lung deflation with the same goal of improving respiratory mechanics. Several randomized controlled trials have confirmed ELVR efficacy in improving lung function, exercise capacity, and quality of life in patients with severe emphysema by using intrabronchial (IBV) or endobronchial valves (EBV).[5-7]

The most common complication observed after valve implantation is pneumothorax, which is seen in 18% to 30% of patients.[7-9] Further complications during long-term follow-up include exacerbation of COPD, distal valve pneumonia, hemoptysis due to granulation tissue formation, and valve displacement with reventilation of the atelectatic lobe and inconsistent therapeutic efficacy.[9,10] Despite significant initial improvements in lung function and exercise capacity, endoscopic therapy has to be terminated in this patient subpopulation.[10] The question, therefore, was whether additional LVRS therapy can be offered to these patients, in particular if they do not meet the standard eligibility criteria for LVRS due to lower-lobe emphysema.

We hypothesized that surgical lung volume reduction (LVRS) would reestablish ELVR short-term clinical improvements after ELVR long-term failure in a selected patient subpopulation with heterogeneous emphysema. Therefore, the present study retrospectively analyzed safety and clinical outcomes of patients initially treated by valve implantation with good clinical benefit, followed by consolidating LVRS by lobectomy of the previously identified target lobe.

Patients and Methods

Study Design

This study was designed as a single-center (Thoraxklinik, Heidelberg University Hospital) retrospective analysis. Patients were selected who underwent LVRS by lobectomy after previously successful, but not of sustained efficacy, ELVR from January 2010 to January 2015. Medical records were carefully reviewed. In this analysis, lung function, exercise tolerance, assessed by the 6-minute walking distance test (6MWD), and scores on the modified Medical Research Council (mMRC) dyspnea questionnaire before and 90 days after ELVR or LVRS were evaluated. ELVR and LVRS were both performed in our hospital, including follow-up. The Heidelberg University Ethics Committee approved the retrospective data analysis (S-174/2019).

Patient Selection

All patients presented with severe heterogeneous emphysema and were eligible for EBV (Zephyr; Pulmonx Corp, Redwood City, CA) or IBV (Spiration; Olympus, Tokyo, Japan) treatment, according to the international recommendations for ELVR.[11] After previous lung function testing by body plethysmography, blood gas analysis, and 6MWD testing, collateral ventilation was excluded by high-resolution computed tomographic (HRCT) scan using fissure analysis. In cases of doubt, an endoscopic assessment of collateral ventilation was performed (Chartis Pulmonary Assessment System, Pulmonx Corp).

All selected patients underwent clinically meaningful target lobe volume reduction (TLVR) after complete occlusion of the treated lobe. The reduced target lobe volume was accompanied by clinically important improvements in lung function or exercise capacity, or both, in all patients. However, for different reasons, the effects of ELVR were not consistent in those patients. ELVR long-term failure was defined as a failure of ELVR therapy after an initial positive therapeutic effect that lasted for at least 3 months. In patients with inconsistent clinical benefit after valve implantation, inadequacy of atelectasis was judged by roentgenogram or low-dose CT. Bronchoscopy was performed if valve dislocation was suspected. In addition, deterioration of lung function was assessed by body plethysmography.

Before each consolidating LVRS, each patient was discussed by an interdisciplinary emphysema board, and surgery was recommended only after a consensus decision. Maximal pharmacotherapy had to be exhausted. A pulmonary rehabilitation or an individual outpatient exercise program, or both, was required in all patients before ELVR or before consolidating LVRS. As a result of the documented positive effect of ELVR, selected patients were also eligible for surgery with a predicted forced expiratory volume in 1 second (FEV_1) of less than 20% or diffusion capacity of the lung for carbon monoxide (D_{LCO}) of less than 20%. A recent HRCT scan and perfusion scintigraphy before LVRS were necessary to identify possible contraindications and to confirm the target lobe once more. The previously identified target lobe was resected through a standard open anterolateral thoracotomy or video-assisted thoracoscopic surgery.

Lung Function Tests

All lung function tests were conducted according to the guidelines of the American Thoracic Society (ATS) and European Respiratory Society (ERS). Body plethysmography, blood gas analysis, D_{LCO}, 6MWD, and assessment with the mMRC dyspnea questionnaire were performed before ELVR or LVRS and further evaluated 90 days after each intervention.

Radiologic Analysis

To evaluate heterogenous emphysema of the lung, a nonenhanced, thin-section, multislice CT scan was performed during an inspiratory breath-hold. To analyze the distribution of emphysema, special in-house software (YACTA ["yet another CT analyzer"]) was applied, which evaluated the resulting 300 to 500 Digital Imaging and Communications in Medicine (National Electrical Manufacturers Association, Rosslyn, VA) images per CT scan to calculate lobe-related lung volume, emphysema index, and mean lung density, as described in detail elsewhere.[12] The automated analysis was performed by a radiologist and is part of our routine workup in all emphysema patients who are evaluated for lung volume reduction.

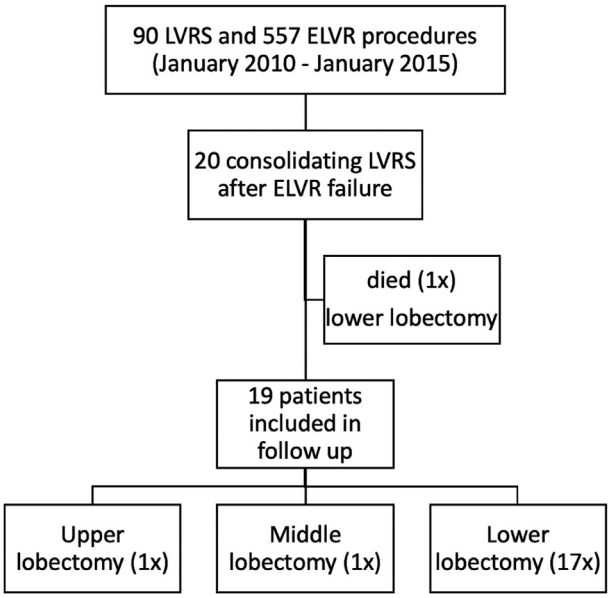

Figure 1. Flowchart of patient selection for consolidating lung volume reduction surgery (LVRS) in a 5-year interval. Lung volume reduction was performed in 647 patients, and LVRS was performed in 14%. Consolidating lung volume reduction by lobectomy after endoscopic lung volume reduction (ELVR) failure was limited to 3.1% of the total cohort.

Responder Analysis

Responder analysis for emphysema-relevant lung function indicators, exercise tolerance, and dyspnea score was performed. According to the literature, the minimal important clinical difference was set for FEV_1 at +12% or more from baseline, for RV at −8.6% or less from baseline, for RV/total lung capacity (TLC) at −4% or less from baseline, and for 6MWD at +26 m or more from baseline, as reported by others.[13-15]

Statistical Analysis

Statistical analysis of the different lung function values, exercise tolerance, and questionnaire point scores was performed with dedicated SigmaPlot 13.0 software (Systat Software, Inc, San Jose, CA). Data are presented as mean ± SD, number, or percentage. Results before and 90 days after LVRS were compared using a Wilcoxon signed rank test. The time patterns of functional changes were statistically analyzed using Friedman repeated-measures analysis of variance on ranks, followed by the Dunn method, as a multiple comparison procedure. *P* values of less than .05 were considered significant.

Results

Study Population and Demographic Characteristics

We retrospectively identified 90 patients with severe emphysema who underwent LVRS from January 2010 until January 2015. During this same interval, ELVR by EBV or IBV implantation was conducted in 557 patients. From both cohorts, 20 patients were identified who underwent LVRS by lobectomy after long-term failure of ELVR (patient flowchart in Figure 1). EBVs were implanted in 12 patients, IBVs in 6 patients, and EBVs and IBVs were both implanted in 2 patients. The interval between ELVR and consolidating LVRS was 19.9 months.

Patients were a mean age 62 years (range, 47-83), and 65% (n = 13) were women (Table 1). Notably, in 90% (18 of 20) of patients, the identified target lobe was the lower lobe. Lobectomy was performed with open thoracotomy in 95% of patients.

This retrospective analysis included 19 of the 20 patients treated with consolidating LVRS by lobectomy. The analysis excluded 1 patient who died before the 90-day follow-up. After an uneventful initial postoperative course, the patient was discharged on day 14 after LVRS. Parapneumonic ipsilateral pleural empyema developed, and the patient had to be readmitted to the hospital. Despite surgical decortication and intensive care therapy, he died 86 days after LVRS of septic multiple organ failure.

The 30-day mortality of the cohort was 0% and 90-day mortality was 5% (1 of 20). The median hospital length of stay was 15 days (interquartile range, 12-17 days). Overall postoperative morbidity was 35%. Major surgery-related complications included respiratory failure that necessitated reintubation and tracheostomy in 1 patient, who was weaned and decannulated before discharge. Additional complications included prolonged air leaks of more than 7 days in 3 patients (15%), reoperation for air leak closure in 1 (5%), myocardial ischemia in 1 (5%), and pneumonia in 3 (15%).

Causes of Valve Treatment Failure and Indication for Surgery

In 14 patients (70%), valve therapy had insufficient long-term therapeutic benefits, which ultimately led to endoscopic valve removal. These included either insufficient atelectasis after valve placement, with only short-term clinical benefit and functional improvement, or recurrent dislocation of the valve by coughing and subsequent reventilation (representative CT images are shown in Figure 2). Recurrent infections developed in 3 patients in the target lobe due to distal valve pneumonia, and hemoptysis developed in 2 patients during the course of therapy due to tissue granulation formation and valve migration. One patient was diagnosed with non-small cell lung cancer (squamous cell carcinoma, pT3 pN0 cM0, stage IIB, *TNM Classification of Malignant Tumours*, Eighth Edition) in the target lobe, and a combined therapeutic approach to lung cancer and emphysema treatment was performed by lobectomy.

Lung Function and Exercise Tolerance After Consolidating LVRS

Baseline values before LVRS and 90 days after are summarized in Table 2. Before consolidating LVRS, the average FEV_1 was 28% predicted, and patients showed severe hyperinflation with an average RV of 280% predicted. Single-breath DLCO was impaired, with 35% predicted. Patients showed limited exercise tolerance, with

Table 1. Characteristics of Patients Assessed Before Long Volume Reduction Surgery, Causes of Endoscopic Lung Volume Reduction Failure, and Indications for Surgery

Variables	Patients (N = 20)
Demographic characteristics	
Sex	
Male	7 (30)
Female	13 (70)
Age, y	62 ± 9
Weight, kg	65 ± 14
Height, cm	165 ± 9
Body mass index, kg/m^2	24 ± 3.6
Location	
Right	5 (25)
Left	15 (75)
Lobe	
Upper	1
Middle	1
Lower	18
Time between ELVR and LVRS, mo	19.9 ± 11.9
Cause of ELVR treatment failure	
Long-term failure of valve treatment	14 (70)
Hemoptysis	2 (10)
Recurrent infections	3 (15)
Lung cancer in the same lobe	1 (5)

Data are presented as number (%) or mean ± SD.

ELVR, endoscopic lung volume reduction; LVRS, lung volume reduction surgery.

an average 6MWD of 273 m. In 12 patients, scores on the valid dyspnea questionnaire were available before surgery, with an average score of 2.9 points.

Significant improvement of lung function was observed 90 days after LVRS in most patients. Vital capacity and FEV_1 were significantly increased by 27%, and RV was diminished by 21%, along with TLC, which was reduced by 11%. This resulted in a significant reduction of the RV/TLC ratio by 13% ± 9%.

Along with lung function, exercise tolerance was significantly improved. Average 6MWD was increased from 273 m to 329 m; additionally, significant improvement in respiratory distress was observed. The mMRC dyspnea score was more than halved 90 days after LVRS.

Responder Analysis

To analyze in detail the clinical relevance of improved lung function and exercise tolerance, an individual responder analysis was performed (Figure 3). Of the 19 patients, 14 were responders (74%) for FEV_1, 15 (79%) for RV, 16 (84%) for RV/TLC, and 67% of patients passed the 6MWD responder threshold.

Time Pattern of Lung Function Before and After ELVR and LVRS

Changes in lung function indicators and exercise tolerance after ELVR and consecutive LVRS therapy over time are summarized in Figure 4. A significant increase in FEV_1 and reduction of lung RV was observed after ELVR therapy. Owing to inconsistent therapeutic effects or removal of valves due to complications, this positive therapeutic effect was completely abolished before LVRS. A significant increase in FEV_1 and reduction of RV were again detectable 90 days after LVRS. The changes after LVRS were approximately equivalent to the changes measured after ELVR therapy.

Comment

This study investigated all patients with emphysema and severe hyperinflation who underwent consolidating LVRS by lobectomy at our institution after ELVR treatment had failed. Here we report the feasibility and outcome of LVRS by lobectomy in patients who had previously been treated by ELVR. We were able to demonstrate that the surgical procedure was associated with acceptable risks in well-selected patients and led to significant improvement in FEV_1, decrease in hyperinflation, and even improvement in exercise capacity.

More than 15 years ago, the National Emphysema Treatment Trial (NETT), the largest multicenter randomized trial on emphysema treatment, demonstrated that LVRS improves lung function, exercise capacity, and long-term survival in patients with upper lobe–predominant emphysema and low exercise capacity.[1,3] Therefore, in many centers, LVRS is considered as a therapeutic option only in this particular patient subgroup.[16] However, single-center studies have shown that these criteria can be extended with respect to comorbidities, such as pulmonary hypertension,[17] impaired diffusion capacity,[18] and nonheterogeneous emphysema distribution.[19] So far, only limited information is available concerning feasibility and outcomes if LVRS is performed in patients after ELVR treatment failure or in terms of combined ELVR and LVRS treatment.

In accordance with NETT criteria, FEV_1 and D_{LCO} values before surgery were above 20% predicted, and therefore, most patients did not meet the criteria of the NETT "high-risk" subgroup.[20] However, 90% of patients in the present investigation presented with lower lobe–predominant heterogeneous emphysema and, therefore, may not be considered ideal candidates for LVRS surgery, according to NETT criteria.

Most of the published studies of high-volume centers report LVRS in upper lobe–predominant heterogeneous emphysema only. In a recent large, single-center analysis published by Ginsburg and colleagues,[21] 91% of patients had upper lobe–predominant emphysema, and a further large retrospective analysis by Horwood and colleagues[22] reported the long-term outcome of 135 patients after LVRS, exclusively diagnosed with upper lobe–predominant emphysema.

The question, therefore, arises why a rather high proportion of patients (90%) were selected for lower-lobe LVRS in the present investigation. One possible explanation for this observation is a generally high rate of the lower lobe being targeted if ELVR is performed compared with LVRS. This was shown in several randomized controlled trials investigating the efficacy of ELVR

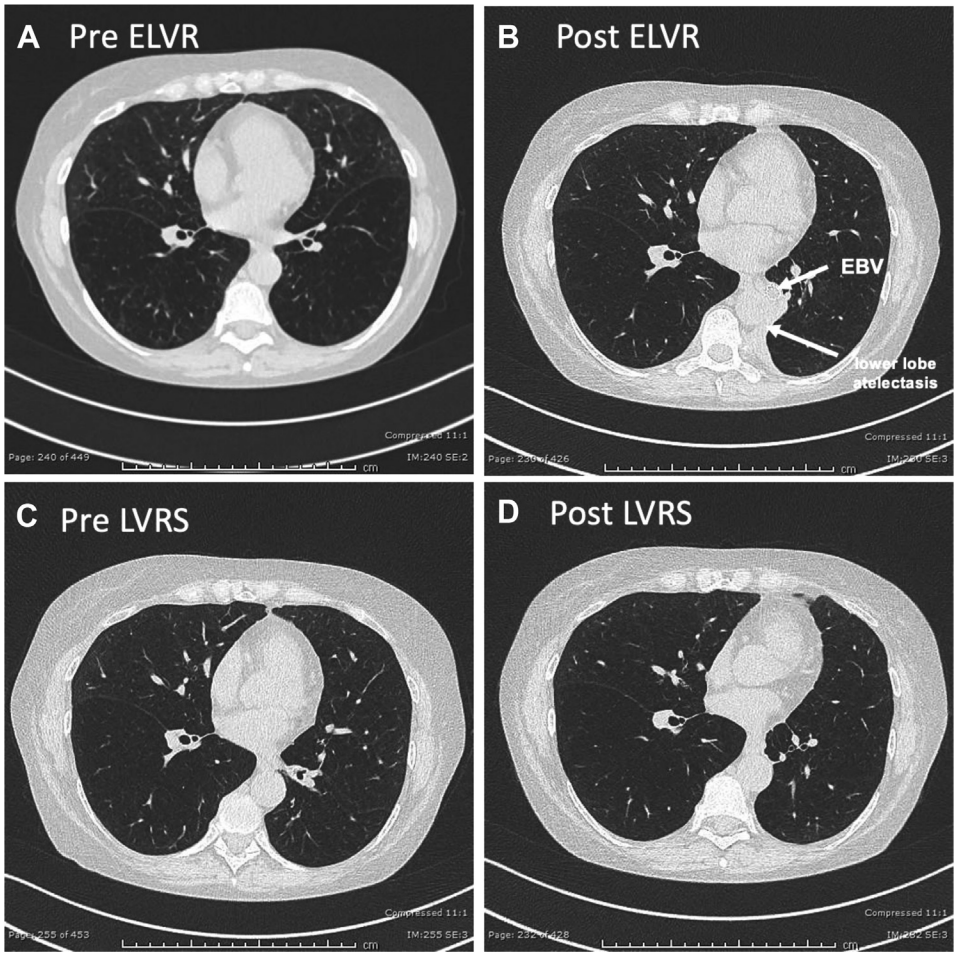

Figure 2. Representative computed tomographic (CT) images of a patient with predominant lower lobe emphysema (A) before endoscopic lung volume reduction (ELVR) therapy and (B) with complete lower lobe atelectasis on the left side after valve implantation with consecutive mediastinal shift to the left. (C) CT scan before lung volume reduction surgery (LVRS) shows reventilation of the left lower lobe caused by recurrent valve dislocation resulting in inconsistent therapeutic effect (D) Follow-up CT scan after left lower lobectomy for consolidating lung volume reduction.

treatment, taking collateral ventilation into account: in the Endobronchial Valves for Emphysema without Interlobar Collateral Ventilation (STELVIO) trial, lower lobes were targeted in 43.8% of cases,[23] in the Improving Patient Outcomes by Selective Implantation of the Zephyr EBV (IMPACT) study in 63%,[7] and in Trial of Endobronchial

Table 2. Analysis of Lung Function, Exercise Tolerance, and Dyspnea

Variable	Pre-LVRS	Post-LVRS (90 d)	Δ% Pre-LVRS	*P* Value[a]
VC, % predicted	66 ± 18	80 ± 17	27.0 ± 33.2	.001
VC, L	2.0 ± 0.6	2.4 ± 0.5	27.4 ± 34.0	.002
FEV_1, % predicted	28.2 ± 5.9	35.5 ± 7.9	27.5 ± 19.4	<.001
FEV_1 , mL	690 ± 150	850 ± 180	24.7 ± 18.5	<.001
RV, % predicted	281 ± 55	216 ± 39	−21.0 ± 17.4	<.001
RV, L	5.8 ± 1.2	4.5 ± 1.0	−21.0 ± 16.2	<.001
TLC, % predicted	147 ± 20	130 ± 17	−11.1 ± 11.1	<.001
TLC, L	7.8 ± 1.4	6.9 ± 1.0	−11.1 ± 11.1	<.001
DLCO SB	35 ± 12	39 ± 12	13.3 ± 7.2	NS
6MWD, m	273 ± 95	329 ± 68	50.0 ± 116	.002
mMRC, points	2.9 ± 1.3	1.2 ± 1.5	−54.9 ± 43.9	.008

[a]$P < 0.05$ vs pre-LVRS by Wilcoxon signed rank test.

Results are given as mean ± SD pre-LVRS and 90 days post-LVRS in 19 patients with follow-up data.

DLCO SB, single breath diffusion capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in 1 second; LVRS, lung volume reduction surgery; mMRC, modified Medical Research Council dyspnea questionnaire; NS, not significant; RV, residual volume; TLC, total lung capacity; VC, vital capacity; 6MWD, 6-minute walking distance.

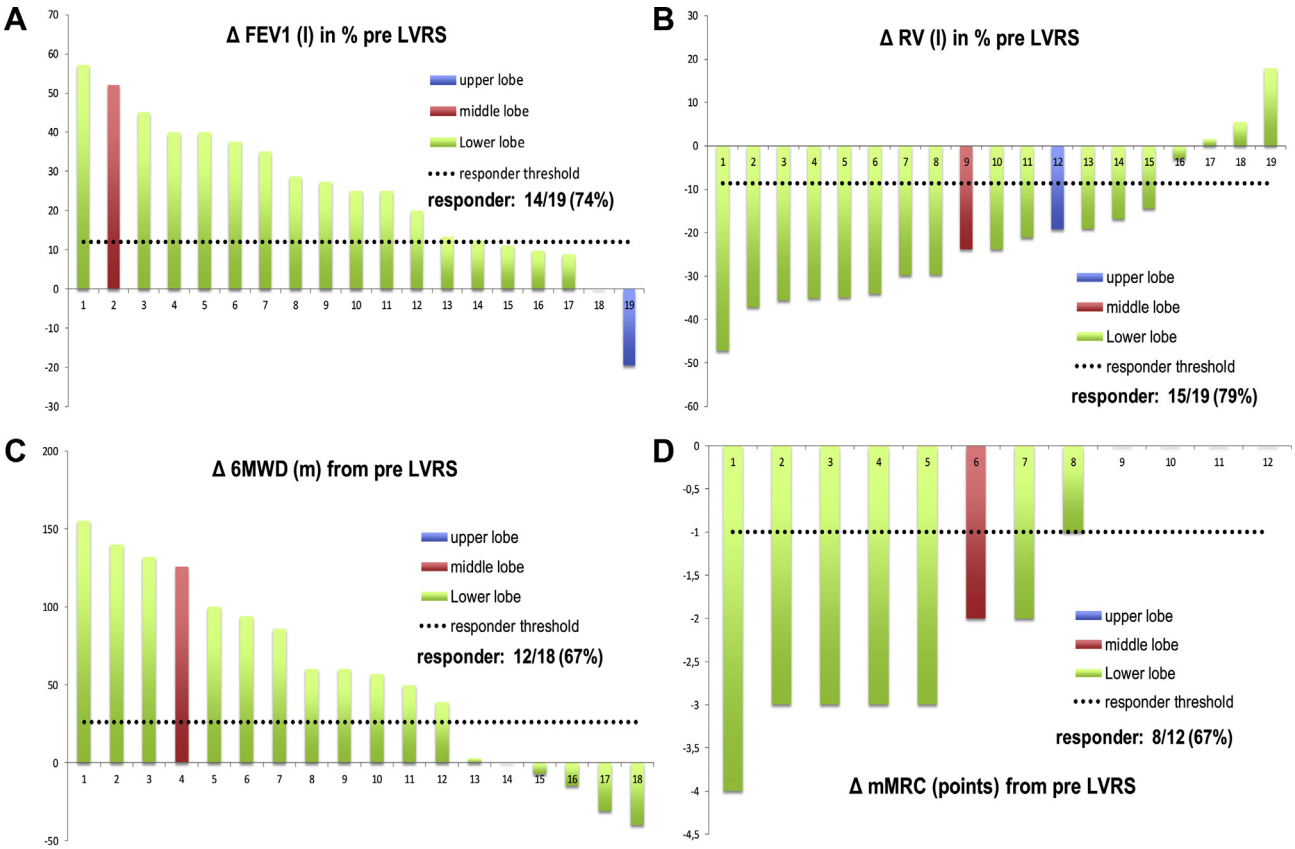

Figure 3. Waterfall-plots of lung function values for (A) forced expiratory volume in 1 second (FEV_1), (B) residual volume (RV), (C) 6-minute walking distance (6MWD), and (D) modified Medical Research Council (mMRC) dyspnea questionnaire, 90 days after lung volume reduction surgery (LVRS) of each individual patient (n = 19) in percentages from pre-LVRS measurements. Responder thresholds according to minimal important clinical differences are given for each indicator as dotted horizontal lines.

Valve Therapy vs. Standard of Care in Heterogeneous Emphysema (TRANSFORM) in 25%.[9]

This rather high rate of endoscopic interventions targeting lower lobes cannot be explained by the distribution of heterogeneous emphysema but must be attributed to a patient selection bias. The selection bias may be explained by the following points: First, the fissure is more often complete on the left side, and therefore, ELVR therapy is more likely to be effective on the left side compared with the right, if collateral ventilation is taken into consideration for adequate patient selection.

Second, the left lower lobe can be endoscopically reached straightforwardly and offers most suitable landing zones for effective valve placement on the segmental level. However, the lower lobe bronchi are softer and less rigid compared with the upper lobe bronchi and, therefore, valve dislocation might be more likely after lower lobe targeting. One could, therefore, hypothesize that ELVR treatment of lower lobes is associated with a higher rate of inconsistent therapeutic effects and long-term treatment failure, compared with upper lobe targeting.

According to the responder analysis, more than two-thirds of patients in the present cohort experienced benefits from consolidating LVRS in all pulmonary function tests and measures of exercise capacity. FEV_1 was increased by 27% and RV was reduced by 1.3 L at 3 months postintervention. A recently published meta-analysis of randomized controlled trials investigating ELVR and LVRS therapy showed a mean increase in FEV_1 of 15.9% and a mean reduction of residual volume by 0.58 L postintervention.[24] The pooled analysis revealed an improvement in 6MWD by 43 m, whereas consolidating LVRS in the present investigation improved 6MWD by 58 m. In their investigation of long-term survival and functional outcomes after lower-lobe LVRS, Perikleous and colleagues[25] showed an approximately equivalent increase in FEV_1 and reduction in the RV/TLC ratio 3 months postsurgery compared with the results in the present study.

In summary, at least equivalent functional improvement was achieved by consolidating lung volume reduction by lobectomy compared with known functional improvements after ELVR therapy or primary LVRS by unilateral or bilateral upper lobe shaving. Our results reveal that LVRS can be performed successfully in patients with lower lobe emphysema. The outcome does not depend on the emphysema distribution to the upper lobes.

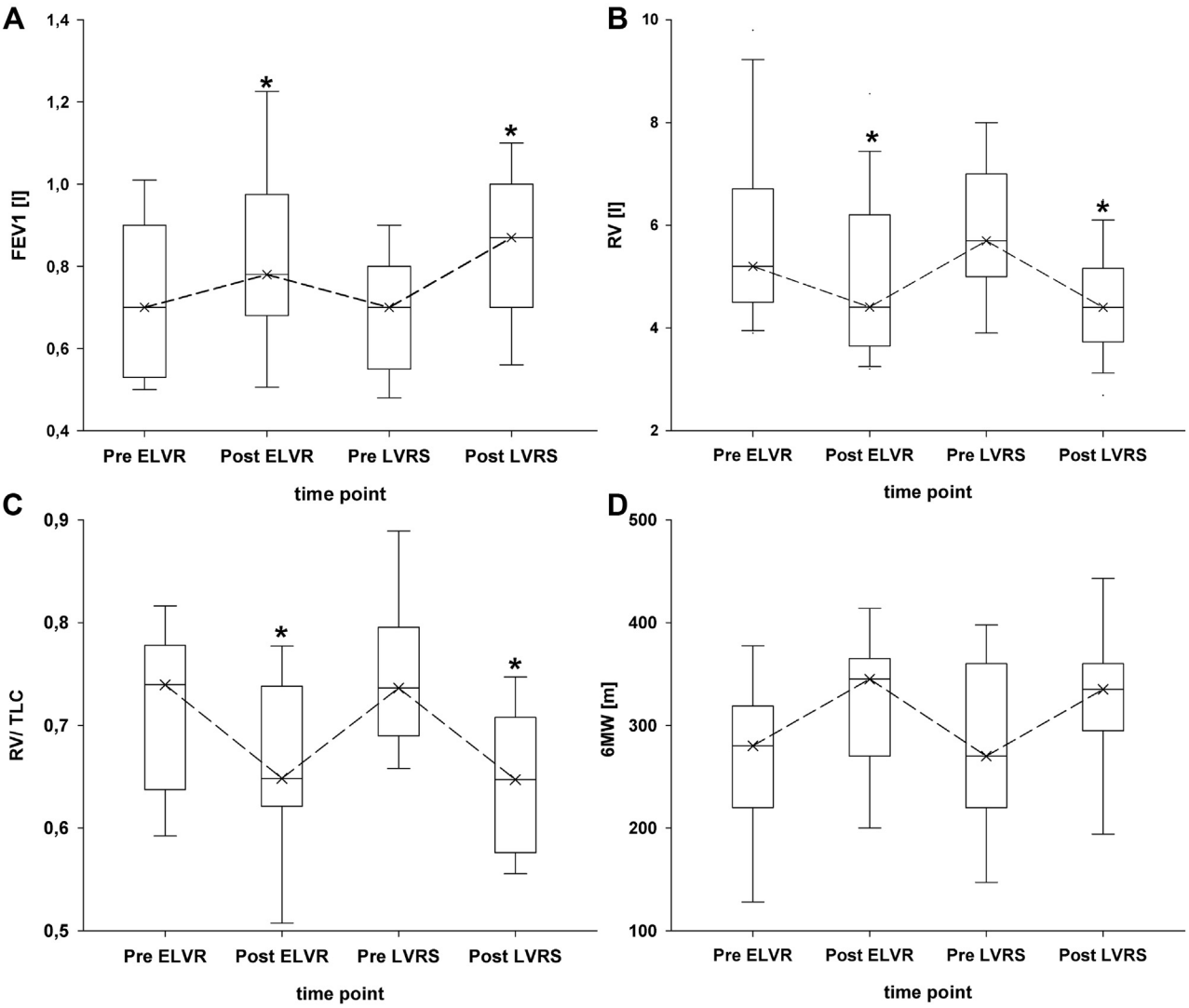

*Figure 4. Time pattern of lung function indicators (A) forced expiratory volume in 1 second (FEV_1) (B) residual volume (RV), (C) RV/total lung capacity (TLC), and (D) exercise tolerance assessed by 6-minute walking distance (6MWD) at baseline (pre) endoscopic lung volume reduction (pre-ELVR) , 90 days after ELVR (post-ELVR), before lung volume reduction surgery (pre-LVRS), and after consolidating LVRS (post-LVRS) by lobectomy. *P < .05 vs pre-ELVR and pre-LVRS, repeated-measures analysis of variance on ranks. The horizontal line in the middle of each box indicates the median; the top and bottom borders of the box mark the 75th and 25th percentiles, respectively, and the whiskers mark the 90th and 10th percentiles.*

Interestingly, the functional improvement after LVRS was equivalent to the temporarily improved lung function and exercise capacity after ELVR therapy. This can be explained by a comparable total lung volume reduction after both ELVR with complete atelectasis and LVRS by lobectomy. Therefore, ELVR therapy by valve implantation may be a useful procedure for predicting functional outcomes after LVRS. Consequently, this strategy will help to further improve patient selection for LVRS therapy, especially if patients do not fulfill the classic NETT selection criteria, because only responders of lung volume reduction will be selected for surgical therapy. Patients who did not show any clinical improvement after ELVR therapy despite significant target lobe volume reduction should not undergo consolidating LVRS.

The main limitations of this study are its retrospective design and lack of a control group to compare the natural course of best medical or interventional treatment. Moreover, the concept of consolidating LVRS is limited to a very small number of highly selected patients.

We therefore conclude that patient selection should be discussed by a multidisciplinary emphysema board and that the center should have extensive experience in both LVRS and ELVR when indications are extended beyond the classical guidelines and patients sequentially undergo both therapeutic modalities. Given the limited treatment options available for this particular patient population, consolidating LVRS can be considered as a promising treatment strategy in patients with

inconsistent therapeutic effects or ELVR long-term failure.

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Looking Forward to Future Outcomes With a Control Group

Invited Commentary:

In this issue of *The Annals of Thoracic Surgery*, the study, titled "Consolidating Lung Volume Reduction Surgery After Endoscopic Lung Volume Reduction Failure," is indeed, a unique article.[1] In almost all series that are published pertaining to lung volume reduction surgery for emphysema, there is a predominance of patients with upper-lobe disease. In fact, it is unusual for upper-lobe disease to not represent more than 90% of the series. In contradistinction, this report is focused on some patients with lower-lobe disease. Also, while generally the surgical approach to lung volume reduction surgery is a bilateral thoracoscopic approach, this group underwent unilateral open lobectomy. As the authors note, this is a highly selected group of patients, and of more than 600 patients who had some treatment for their emphysema, this study focused on only 19 patients. The study, itself, is entirely retrospective and without a control group.

It should be noted that they started with a fairly ideal group of patients, who had heterogeneous disease and were very hyperinflated. The group's mean residual volume was 280%. One would expect excellent results with volume reduction, no matter what the form of treatment was, with this group.

Overall, in their entire group of patients that they put bronchial valves in to treat emphysema, more than 50% were placed in the lower lobes. It seems like a

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