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Repeated lung volume reduction surgery is successful in selected patients†

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Abstract

OBJECTIVES: Lung volume reduction surgery (LVRS) improves dyspnoea, quality of life and may even prolong survival in carefully selected patients with end-stage emphysema. The benefit may be sustained for several years and vanishes with the natural progression of the disease. Data on repeated surgical treatment of emphysema are scarce. The aim of this study was to evaluate the safety, effects and outcomes of repeated LVRS (Re-LVRS) in patients no longer benefiting from their initial LVRS.

METHODS: Between June 2002 and December 2013, 22 patients (9 females) with advanced emphysema underwent Re-LVRS at a median of 60 months (25–196) after their initial LVRS. While initial LVRS was performed thoracoscopically as a bilateral procedure, Re-LVRS was performed unilaterally by a video-assisted thoracoscopic technique in 19 patients and, due to adhesions, by thoracotomy in 3 patients. Pulmonary function test (PFT) was performed at 3 and 12 months postoperatively.

RESULTS: Lung function at Re-LVRS was similar to that prior to the first LVRS. The 90-day mortality rate was 0%. The first patient died 15 months postoperatively. The median hospitalization time after Re-LVRS was significantly longer compared with the initial LVRS [14 days, interquartile range (IQR): 11–19, vs 9 days, IQR: 8–14; $P = 0.017$]. The most frequent complication was prolonged air leak with a median drainage time of 11 days (IQR: 6–13); reoperations due to persistent air leak were necessary in 7 patients (32%). Five patients (23%) had no complications. Lung function and Medical Research Council (MRC) score improved significantly for up to 12 months after Re-LVRS, with results similar to those after initial bilateral LVRS. The average increase in the forced expiratory volume in 1 s (FEV1) was 25% (a 7% increase over the predicted value or 0.18 l) at 3 months, and the mean reduction in hyperinflation, assessed by relative decrease in RV/TLC (residual volume/total lung capacity), was 12% at 3 months (a decrease of 8% in absolute ratios). The mean MRC breathlessness score decreased significantly after 3 months (from 3.7 to 2.2).

CONCLUSIONS: Re-LVRS can be performed successfully in carefully selected patients as a palliative treatment. It may be performed as a bridge to transplantation or in patients with newly diagnosed intrapulmonary nodules or during elective cardiac surgery. Morbidity is acceptable and outcomes may be satisfactory with significantly improved lung function and reduced dyspnoea for at least 12 months postoperatively.

Keywords: Lung volume reduction surgery • End-stage pulmonary emphysema • Lung volume reduction • Reoperation

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a leading global health problem and is predicted to be the third largest cause of death worldwide by 2020 [1]. It leads to emphysematous destruction of the lung parenchyma and therefore causes dyspnoea as well as rapid loss of physical fitness and quality of life [2].

Lung volume reduction surgery (LVRS) is a successful and well-established palliative treatment for end-stage emphysema in carefully selected patients. Several randomized controlled trials have confirmed the feasibility of surgical therapy and that it is superior to best medical treatment in long-term survival and exercise capacity in a specific subgroup of patients [3–6].

The pathophysiology of severe emphysema includes hyperinflation and small airway obstruction through parenchymal destruction, thereby allowing the possibility of mechanical repair. By surgically removing the most affected areas of lung parenchyma, hyperinflation is reduced and diaphragm and chest wall

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mechanics are improved. Furthermore, small airway obstruction can be reduced by an increase of elastic recoil forces [7].

The effects of LVRS may last for up to 5 years, depending on the morphology of the emphysema [8, 9]. Surgery itself does not modify the subsequent natural history of the disease [3] and, as the natural history of emphysema and the annual decline in pulmonary function take their course, lung function and dyspnoea return to pre-LVRS levels after a certain period that differs from person-to-person [4].

The only treatment that can stop the progressive course of the disease is bilateral lung transplantation. In some patients, it may be feasible to use LVRS as a bridge to transplantation [10–12]; however, many patients with end-stage COPD do not qualify for transplantation because of advanced age or comorbidities, and therefore LVRS has been described as a successful alternative in appropriately selected patients [11, 13, 14].

Recent data from the Society of Thoracic Surgeons database suggests a limited use of LVRS in the USA, with an initial increase of LVRS performed after data from the National Emphysema Treatment Trial were published but with numbers remaining steady since 2004 [15]; data for Europe are, unfortunately, not available, but again a limited use can be assumed. However, many patients treated by LVRS survive the duration of the positive effect and re-experience the loss of quality of life despite receiving optimal medical treatment. For those not eligible for transplantation, a limited range of therapeutic options remain.

Repeated LVRS (Re-LVRS) is a technically and also medically challenging procedure that targets the ongoing parenchymal destruction. Data regarding the feasibility and safety of Re-LVRS are scarce. However, a first case was described by Stammberger *et al.* in 2000 [16], after which the beneficial effects of Re-LVRS on pulmonary function and quality of life were shown in a small population of 16 patients [17]. However, while it was technically feasible and led to overall improvements, the reported mortality rate was as high as 11.7%, rendering it a high-risk operation [17].

The aim of this retrospective study was to further evaluate the morbidity and mortality, as well as the efficacy and outcome, due to Re-LVRS in carefully selected patients after cessation of the beneficial effects of initial LVRS, to elucidate the role of repeated surgery in this high-risk population.

MATERIALS AND METHODS

Patient selection

Inclusion criteria were adapted from our modified patient selection criteria for initial LVRS [7]. Patients eligible for Re-LRVS had to have experienced a significant improvement of dyspnoea and pulmonary function test after the initial LVRS, but had to present with a deterioration of their dyspnoea [measured by Medical Research Council (MRC) dyspnoea score] and pulmonary function tests (PFTs) to levels similar to the pre-LVRS level. In addition to severe airflow obstruction (FEV1 < 35%), hyperinflation of the lung (TLC > 120%, RV > 200%, RV/TLC > 65) and sustained minimum diffusion capacity (DLCO > 20%), the patients selected for Re-LVRS had to be highly motivated for a repeated operation.

CT scans had to reveal either heterogeneous to intermediately distributed marked areas of emphysematous destruction, or newly diagnosed intrapulmonary nodules suspicious for malignancy. Patients with significant comorbidities, like coronary artery disease or pulmonary hypertension, were excluded.

Preoperative assessment

Prior to the operation, rigorous testing was performed to verify operability. In addition to recent PFTs and chest CT scans with densitometry, a radionuclide lung perfusion scan was performed to identify the most affected areas. To further evaluate operability, myocardial SPECT was performed in patients with uncertain myocardial function ($n = 7$, 32%).

The MRC dyspnoea score, a simple and valid score that consists of five categories (0–4), and which has been shown to correctly categorize disability in COPD patients [18], was used to categorize the physical disability of the patients due to COPD.

Decisions on reoperation were taken according to our inclusion/exclusion criteria by an interdisciplinary committee consisting of thoracic surgeons, pulmonologists and radiologists.

Surgery

Re-LVRS was performed unilaterally by video-assisted thoracoscopy surgery (VATS) in 19 patients, and in 3 patients by thoracotomy due to adhesions from the previous LVRS or infection; 1 patient had a bilateral Re-LVRS (Table 1). The areas of pulmonary parenchyma exhibiting greatest destruction were resected using standard staplers (COVIDIEN Endo GIA™ Ultra Universal, ETHICON Echelon ENDOPATH™) without buttressing (for both, initial LVRS and Re-LVRS).

Follow-up and outcome measures

All PFTs were performed using a standard body plethysmograph and CO diffusion capacity (Zahn, Germany). The follow-up included PFT and MRC dyspnoea score at baseline and 3 and 12

Table 1: Patient specifics

	Age, years (IQR)	Bilateral procedure (*n*)		Unilateral procedure (*n*)		Additional information (*n*)
		Thoracoscopy	Thoracotomy	Thoracoscopy	Thoracotomy	
Initial LVRS	59 (55–67)	20	–	1	1	Suspicious nodule: 1
Re-LVRS	65 (62–72)	–	1	19	2	Transplantation waiting list: 2 Suspicious nodules: 4 Elective cardiac surgery: 1

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months after surgery. The success of the procedure was judged by (i) reduction of hyperinflation assessed by a decrease in residual volume (RV), total lung capacity (TLC) and their ratio (RV/TLC), (ii) increase in forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1) and diffusion capacity of the lung for carbon monoxide (DLCO), and (iii) reduction of dyspnoea assessed by the MRC score. Patients with suspected or proven malignancy had regular CT scans for the cancer follow-up.

Complete data sets of PFT are available for 22 (100%), 21 (95%) and 14 patients (64%) after LVRS and for 22 (100%), 11 (50%) and 9 patients (41%) after Re-LVRS at baseline, 3 and 12 months after the operation, respectively.

Statistical analysis

All values are displayed as the mean ± standard error or median and interquartile range (IQR), unless otherwise stated. Descriptive statistical analysis was performed comparing perioperative morbidity and duration of hospitalization. PFT at 3 and 12 months after either LVRS or Re-LVRS were compared with baseline values using a two-tailed paired samples *t*-test. For evaluation between the LVRS and the Re-LVRS group the Wilcoxon matched-pair signed-rank test was used for continuous variables and McNemar's test for categorical variables.

A *P*-value of <0.05 was determined as significant (*), and $P < 0.001$ as highly significant (**). All data were produced using SPSS (IBM Corp., Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY, USA: IBM Corp.). Graphs were plotted using GraphPad Prism version 4.0c for Macintosh (GraphPad Software, San Diego, CA, USA).

RESULTS

Between June 2002 and December 2013, 22 patients (9 females) with a median age of 65 years (IQR: 62–72) underwent repeated LVRS (Re-LVRS) for the following reasons: (i) cessation of the beneficial effects of initial LVRS only ($n = 15$); (ii) tissue-diagnosis and treatment of newly diagnosed intrapulmonary nodules ($n = 4$); (iii) as a bridge to transplantation ($n = 2$) or (iv) during elective cardiac surgery ($n = 1$) (also see Table 1). The median time span between initial and repeated LVRS was 60 months (range: 25–196). During the same period (between June 2002 and December 2013) 303 patients underwent first-time LVRS, which means that 7% of all LVRS performed during this time were Re-LVRS.

The morphology of the emphysema for initial LVRS was heterogeneous in 17 patients (77%), intermediate in 3 patients (14%) and homogeneous in 2 patients (9%) according to Weder *et al*. in 1997 [19]. CT morphology had changed in 2 patients from a markedly heterogeneous to an intermediate type after initial LVRS. Initial LVRS was performed mostly bilaterally including upper lobes ($n = 17$, 77%), while Re-LVRS was performed unilaterally in all but 1 patient and lower lobes were operated on more frequently (Table 2). In 14 patients (64%) the same lobe was operated, 6 patients had lung resections in a different lobe (27%), and 2 patients had resections in the same and a different lobe (9%). Severe adhesions were significantly more frequent in Re-LVRS compared with initial LVRS (8 vs 2, $P = 0.031$) and no relevant adhesions were present significantly more often during initial LVRS (18 vs 7, $P = 0.001$).

The perioperative and 90-day mortality rate was 0% (Table 3); the first patient died 15 months postoperatively. The median hospitalization time was significantly longer for Re-LVRS compared

Table 2: Operated lobes for initial LVRS and Re-LVRS. Numbers shown are absolute patient numbers.

	Upper lobe			Lower lobe			Combined		Middle lobe
	Bilateral	Unilateral		Bilateral	Unilateral		2 Ipsilateral	>2 Bilateral	
		Left	Right		Left	Right			
Initial LVRS	15	–	2	1	–	–	–	4	–
Re-LVRS	1	3	6	–	5	2	4	–	1
	Same lobe			Different lobe			Same + different lobes		
Re-LVRS	14			6			2		

Table 3: Hospitalization specifics and perioperative morbidity and mortality for initial LVRS and Re-LVRS

	Initial LVRS	Re-LVRS	Wilcoxon matched-pair signed-rank test (*P*-value)
Hospitalization time (IQR)	9 (8–14)	14 (11–19)	0.017
Drainage time (IQR)	6 (4–10)	11 (6–13)	0.050
			McNemar's test (*P*-value)
Overall complications, *n* (%)	10 (45)	17 (77)	0.092
Pulmonary complications	9 (41)	16 (73)	0.092
Prolonged air leak	8 (38)	14 (64)	0.180
Pneumothorax	1 (4.5)	2 (9)	1.0
Operative revision	2 (9)	7 (32)	0.125
Cardiac complications	1 (4.5)	2 (9)	1.0
Perioperative mortality	0	0	–

Table 4: Pulmonary function tests before and 3 and 12 months after initial LVRS and Re-LVRS

Parameter	Before initial LVRS	3 months after LVRS	12 months after LVRS	Pre-Re-LVRS	3 months after Re-LVRS	12 months after Re-LVRS
FVC (l)	2.4 ± 0.13	3.32 ± 0.2**	2.98 ± 0.3**	2.4 ± 0.13	2.7 ± 0.14*	3.0 ± 0.3*
FVC (%)	69 ± 3.6	90.5 ± 3.7**	88.1 ± 6.5**	70 ± 4.4	80 ± 4.5*	82 ± 6.4*
FEV1 (l)	0.79 ± 0.05	1.3 ± 0.1**	1.03 ± 0.1*	0.72 ± 0.04	0.9 ± 0.06*	0.9 ± 0.1*
FEV1 (%)	27.8 ± 1.8	45 ± 3.0**	36 ± 3.5*	28.6 ± 3.0	34.8 ± 3.0*	31 ± 2.6*
RV (l)	5.55 ± 0.29	4.00 ± 0.2**	4.2 ± 0.3**	5.6 ± 0.3	4.2 ± 0.4*	4.2 ± 0.4
RV (%)	255 ± 12	181 ± 9.4**	185 ± 11**	237 ± 14	182 ± 22*	168 ± 28
TLC (l)	8.4 ± 0.3	7.7 ± 0.3*	7.8 ± 0.4*	7.7 ± 0.4	7.17 ± 0.4	7.4 ± 0.8
TLC (%)	138 ± 5	125 ± 3.2*	127 ± 3.4*	135 ± 5.1	118 ± 7.1*	112 ± 10
RV/TLC (%)	66 ± 2	52 ± 1**	53 ± 2**	68 ± 2	60 ± 3*	56 ± 3*
DLCO (%)	41 ± 2.4	48 ± 3.0	47 ± 2.7	35 ± 2.5	34 ± 2.2	41 ± 6
MRC scale [0–4]	3.3 ± 0.1	0.85 ± 0.2**	1.4 ± 0.26**	3.7 ± 0.1	2.2 ± 0.2*	1.0 ± 0.7

DLCO: diffusion capacity of the lung for carbon monoxide; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; RV: residual volume; TLC: total lung capacity
Mean ± standard error. *$P < 0.05$;
**$P < 0.001$ compared with preoperative values.

with initial LVRS (14 days, IQR: 11–19 vs 9 days, IQR: 8–14, $P = 0.017$). The overall complication rate was lower, though not statistically significant, for LVRS compared with Re-LVRS (45 vs 77%, $P = 0.092$). Prolonged air leak accounted for the most frequent cause of morbidity in both groups but did not reach statistical significance (36 vs 64%, $P = 0.092$). Surgical revisions were three times more frequent after Re-LVRS than after initial LVRS, but did not reach statistical significance (32 vs 9% patients, $P = 0.125$). Other morbidities are summarized in Table 3.

Levels of pulmonary function and subjective dyspnoea at the time of reoperation were similar to levels prior to the initial operation (Table 4). Pulmonary function tests and dyspnoea score (MRC breathlessness scale) were assessed 3 and 12 months after Re-LVRS, showing significant overall improvement of lung function with improved FEV1 (Fig. 1), improved diffusion capacity (Fig. 2), reduction in hyperinflation assessed by RV/TLC (Fig. 3) as well as reduced dyspnoea assessed by the MRC score (Fig. 4) both after initial and Re-LVRS (see Table 4).

After Re-LVRS the mean increase in FEV1 was 25 and 12% from baseline (absolute increase of 7 and 3.2% of the predicted value corresponding to 0.18 and 0.18 l) at 3 months and 12 months, respectively, compared with 62 and 29% (absolute increase of 17.2 and 8.2% of the predicted value corresponding to 0.5 and 0.24 l) after initial LVRS (also see Fig. 1). The mean reduction in pulmonary hyperinflation, assessed by the decrease in RV/TLC, was 8 and 13%, and 14 and 13% from the baseline at 3 and 12 months for Re-LVRS and initial LVRS, respectively. LVRS thereby showed a more pronounced increase of FEV1 ($P = 0.022$), reduction of hyperinflation assessed by RV/TLC ($P = 0.008$) as well as a lower MRC score ($P = 0.033$) when compared with Re-LVRS at 3 months. These differences were not detectable at 12 months.

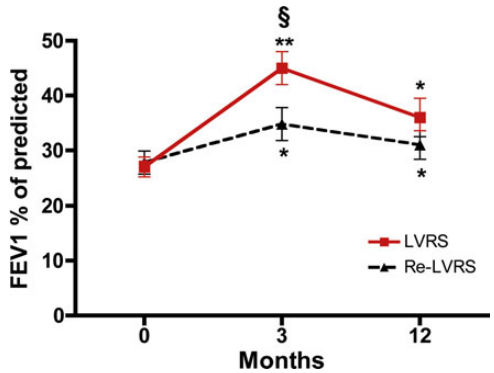

Figure 1: Course of FEV1 (% of predicted) preoperative (0), 3 and 12 months for initial LVRS and Re-LVRS. *$P < 0.05$, **$P < 0.001$ for 3 and 12 months compared with baseline. $^{\S}P < 0.05$ for LVRS vs Re-LVRS. FEV1: forced expiratory volume in 1 s.

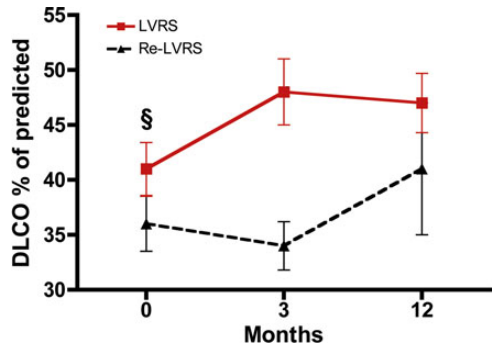

Figure 2: Course of DLCO (% of predicted) preoperative (0), 3 and 12 months for initial LVRS and Re-LVRS. Changes at 3 and 12 months not significant compared with baseline. $^{\S}P < 0.05$ for LVRS vs Re-LVRS. DLCO: diffusion capacity of the lung for carbon monoxide.

DISCUSSION

In this retrospective study, we evaluated the safety, feasibility and effects of repeated LVRS (Re-LVRS) in 22 carefully selected patients.

The question of further treatment options after the beneficial effects of an initially successful LVRS have vanished is raised frequently in clinical practice; even though LVRS seems to be broadly underused in Europe as well as the USA, patient numbers are at least stable [15]. As ongoing parenchymal destruction and the natural course of the disease continue at individual rates, the time span towards deterioration to initial exercise ability varies between patients and emphysema type [9], but positive effects may last for up to 5 years. After this individual time span the patients

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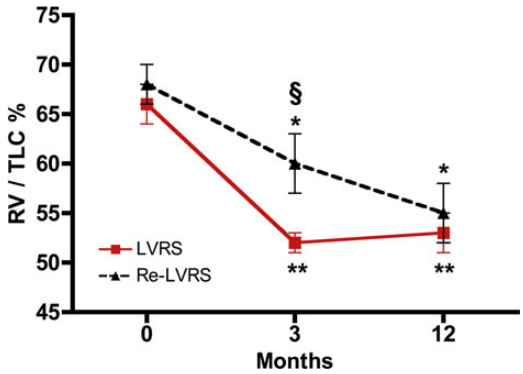

Figure 3: Course of RV/TLC (%) preoperative (0), 3 and 12 months for initial LVRS and Re-LVRS. *$P < 0.05$, **$P < 0.001$ for 3 and 12 months compared with baseline. $^{§}P < 0.05$ for LVRS vs Re-LVRS. RV: residual volume; TLC: total lung capacity.

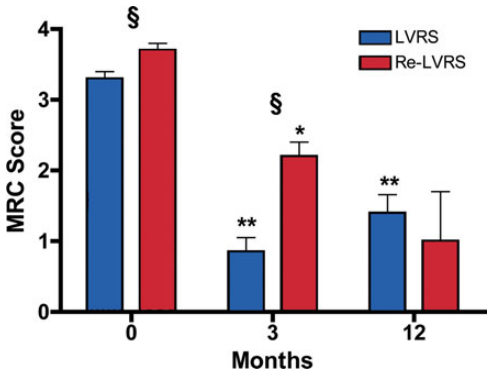

Figure 4: MRC dyspnoea score for preoperative (0), 3 and 12 months for initial LVRS and Re-LVRS. *$P < 0.05$, **$P < 0.001$ for 3 and 12 months compared with baseline. $^{§}P < 0.05$ for LVRS vs Re-LVRS. MRC score: Medical Research Council score.

re-experience the loss of physical fitness and quality of life and, for those not eligible for transplantation, treatment options are very limited.

Re-LVRS has so far been reported in a case report as well as in one small retrospective study; beneficial effects of Re-LVRS were suggested in some patients [16, 17]. However, high mortality and morbidity were reported, particularly due to the high-risk population of end-stage emphysema patients in the setting of a reoperation, with a higher incidence of ARDS in these patients compared with the first-time LVRS population [17].

In our cohort of 22 patients, the preoperative lung function values had decreased to levels similar to that before the initial LVRS, and repeated LVRS was performed after a median time of 60 months. Improvements in lung function after unilateral, thoracoscopic Re-LVRS were statistically significant compared with baseline and showed a similar extent at 12 months compared with the initial LVRS. However, beneficial effects were more pronounced after initial LVRS compared with Re-LVRS at 3 months. The reduction in hyperinflation as well as subjective dyspnoea was comparable with data published by Taccconi *et al*. [17]. Reoperations were technically feasible, and all but three were performed by VATS. Not surprisingly, overall morbidity was lower after the initial LVRS compared with Re-LVRS (operative revisions were necessary three times more frequently in the latter; also see Table 3), but these differences were not statistically significant. The complication rate stayed within an acceptable range and was comparable with international data after LVRS [3–6, 15]. In contrast to a previous report of Re-LVRS, we observed no perioperative mortality or ARDS in our cohort.

The 90-day mortality rate of 0% may be explained, to some extent, by rigorous selection of candidates and high surgical expertise (all operations were performed by the same surgeon (Walter Weder) as well as anaesthesia and ICU management. Other important factors include optimal medical treatment as well as intensive physiotherapy and pulmonary rehabilitation programmes and a multidisciplinary approach [20].

Re-LVRS successfully treated the disabling dyspnoea in this population of 22 patients; however, the small number of patients and limited availability of complete data sets limit the validity of this study to some extent. Moreover, the retrospective design may have resulted in a selection bias. To shed more light on the question of safety and efficacy, prospective analysis of a bigger patient population in a prospective manner is needed. However, this small study proves that Re-LVRS is an option and should be considered in selected patients.

While small numbers limit the validity of the study as a whole, each patient represents their own control group; first, because they had already proved to benefit from LVRS due to the specific pathophysiological mechanisms of their disease, and secondly, because lung function had deteriorated to a pre-LVRS level despite administration of optimal medical treatment. A repeated gain in lung function after Re-LVRS therefore may work by the same mechanisms as initial LVRS and might be superior to the best medical treatment in some patients. Hence, a previous LVRS should not be considered as a contraindication to perform Re-LVRS and patients should be selected according to the same criteria. For safety reasons and due to the fact that DLCO was lower compared with the first intervention, we decided to perform Re-LVRS unilaterally only.

End-stage emphysema remains an incurable disease and no medical treatment has been shown to influence the course of the disease; therefore the only definitive treatment for patients previously treated by LVRS is lung transplantation. However, considering the limited donor availability and high mortality rates on the waiting list [12], Re-LVRS can be considered as a bridge to transplantation in younger patients and as a final treatment in elderly patients or those otherwise not eligible for transplantation.

In conclusion, our findings emphasize that Re-LVRS is safe to be performed in carefully selected patients and may lead to significantly reduced dyspnoea and improved lung function for at least 12 months postoperatively. A previous LVRS should therefore not be considered a contraindication for LVRS, and the same patient selection criteria should be applied.

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Conflict of interest: none declared.

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