Respiration

Interventional Pulmonology

Respiration 2025;104:281–289
DOI: 10.1159/000542806

Received: June 15, 2024
Accepted: November 20, 2024
Published online: November 25, 2024

Comparison of Efficacy and Safety of Different Types of One-Way Valves in Endoscopic Lung Volume Reduction in Patients with Severe Lung Emphysema

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Keywords
Endoscopic lung volume reduction · Lung emphysema

Abstract

Introduction: Endoscopic lung volume reduction (ELVR) with valves is an effective intervention in patients with severe lung emphysema. Two types of valves are established in clinical practice: Zephyr endobronchial valves (EBVs) and Spiration Valve System (SVS). We aimed to compare outcomes and the safety associated with these two types of one-way valves. ***Methods:*** Data were collected from three German lung emphysema centers as part of a prospective observational study focusing on lung volume reduction. Two groups were formed based on valve types. In both groups, lung function (FEV_1, RV, diffusion capacity of the lung for carbon monoxide, pCO_2), 6-min walking distance (6MWD), quality of life (SGRQ, mMRC, CAT), and complication rate were recorded at baseline and at follow-up 3 to 6 months later. ***Results:*** A total of 54 patients were treated with SVS valves and 99 patients with EBV. There were no significant differences between both groups at baseline. Notably, both types of valves exhibited significant enhancements in lung function and quality of life. Interestingly, there were no significant differences in the median change of all measured parameters for both groups, suggesting comparable improvements in EBV and SVS. Pneumothorax was the most common complication for both valve types. The incidence of adverse events did not differ significantly between groups. ***Conclusion:*** Our study suggests that both types of valves are safe and effective in the treatment of severe lung emphysema. We recommend choosing the valve type based on individual bronchial anatomy. However, further randomized studies are needed to confirm our results.

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading and growing cause of worldwide morbidity and mortality [1–3]. In the year 2017 alone, 3.2 million deaths due to COPD were recorded, making COPD the third leading

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cause of death worldwide [4]. An especially severe form of COPD is the development of advanced lung emphysema. Chronic inflammation in the small airways causes remodeling and narrowing of the airway walls. This inflammation is frequently due to inhaling noxious fumes, with cigarette smoke being the most common cause for the development of COPD [5, 6]. These pathophysiological mechanisms underlying chronic inflammation lead to air entrapment within the narrower airways in the small alveoli [7]. Over time, this causes the destruction of the alveolar walls, resulting in hyperinflation and potentially severe limitations to gas exchange [1, 8]. For this reason, patients with COPD and severe lung emphysema often suffer from severe dyspnea, exercise intolerance, and a reduced quality of life [9].

Lung volume reduction therapy has become a treatment option for a highly selected group of patients suffering from advanced forms of lung emphysema and can lead to significant improvements in lung function, exercise capacity, and quality of life of these patients [10, 11]. In a highly selected group of patients, lung volume reduction can lead to significant improvements in lung function, exercise capacity, and quality of life. The process of endoscopic lung volume reduction (ELVR) with one-way valves was established in clinical practice after several high-profile randomized controlled trials (RCTs) demonstrated positive outcomes and a good safety signal, among these RCTs being the LIBERATE and EMPROVE studies [11–18]. However, one-way valves of different manufacturers were used in these studies, either Zephyr endobronchial valves (EBVs; Pulmonx®, Redwood City, CA, USA) featuring a duckbill design or the intrabronchial Spiration Valve System (SVS; Olympus®, Center Valley, PA, USA) featuring an umbrella design.

To our knowledge, no systematic analysis has been published previously regarding potential differences or similarities in outcome between these two valve types. Consequently, clinicians choose between the valve types relying on personal experience and availability, rather than on scientific evidence. This study employed real-world data provided by three lung emphysema centers in the German lung emphysema registry (LE-Registry), which chose from the two valve types based on bronchial anatomy. We examined whether patients treated with the EBV or SVS experienced comparable clinical benefits and risk profiles for adverse events.

Methods

All analyzed data were obtained from three centers in the German LE-Registry (www.lungenemphysemregister.de). This registry is an open-label multicenter prospective clinical study, which focuses exclusively on patients with severe lung emphysema undergoing a form of lung volume reduction. The stated goal of the registry is to assess and compare outcomes after different types of lung volume reduction independent of any third party. For this analysis, we did not use the whole database but focused on three centers, all of which use both types of valves ad libitum. These centers are the Charité – Universitätsmedizin Berlin, the Gemeinschaftskrankenhaus Havelhöhe, and the Lungenklinik Hemer. Both the Charité – Universitätsmedizin Berlin and Gemeinschaftskrankenhaus Havelhöhe are founding members of the LE-Registry and started including patients in 2017. The Lungenklinik Hemer first patients were included in the LE-Registry in 2020. Data were collected until the eleventh of February 2024.

The ethic approval for the study was given by the Local Ethics Committee of Charité – Universitätsmedizin Berlin under the registration number: EA2/149/17. A written informed consent was obtained from every patient prior to the enrollment in the study.

Inclusion and Exclusion Criteria

Inclusion and exclusion criteria were previously described [19, 20]. Patients had to fulfill the following parameters to be eligible for inclusion in this study: forced expiratory volume in 1 s (FEV_1) ≤45% of predicted value, residual volume (RV) ≥180% of predicted value, partial pressure of carbon dioxide (pCO_2) <55 mm Hg, and 6-min walk distance (6MWD) ≤450 m. Prior to ELVR, they had to receive optimal pharmacological treatment of COPD and provide a proof of smoking abstinence over 3 months (no cotinine levels in urine or carboxyhemoglobin <2%). Additionally, all patients had to receive an assessment of collateral ventilation by Chartis® (Pulmonx, Redwood City, CA, USA) and/or by software-dependent analysis of fissure integrity (StratX Platform [Pulmonx, Redwood City, CA, USA] or VIDA Vision [VIDA Diagnostics, Coralville, IA, USA]) [21–23].

Exclusion criteria were age below 40 years, inability to provide informed consent, or missing documentation of the valve type used. 15 patients who received both types of valves were also excluded from this study. The respective treatment for each patient was discussed and determined in local multidisciplinary conferences consisting of experienced pulmonologists, thoracic surgeons, and radiologists.

Only those patients were included in this study who received ELVR with one-way valves. These were split into two groups based on the type of valve used in the

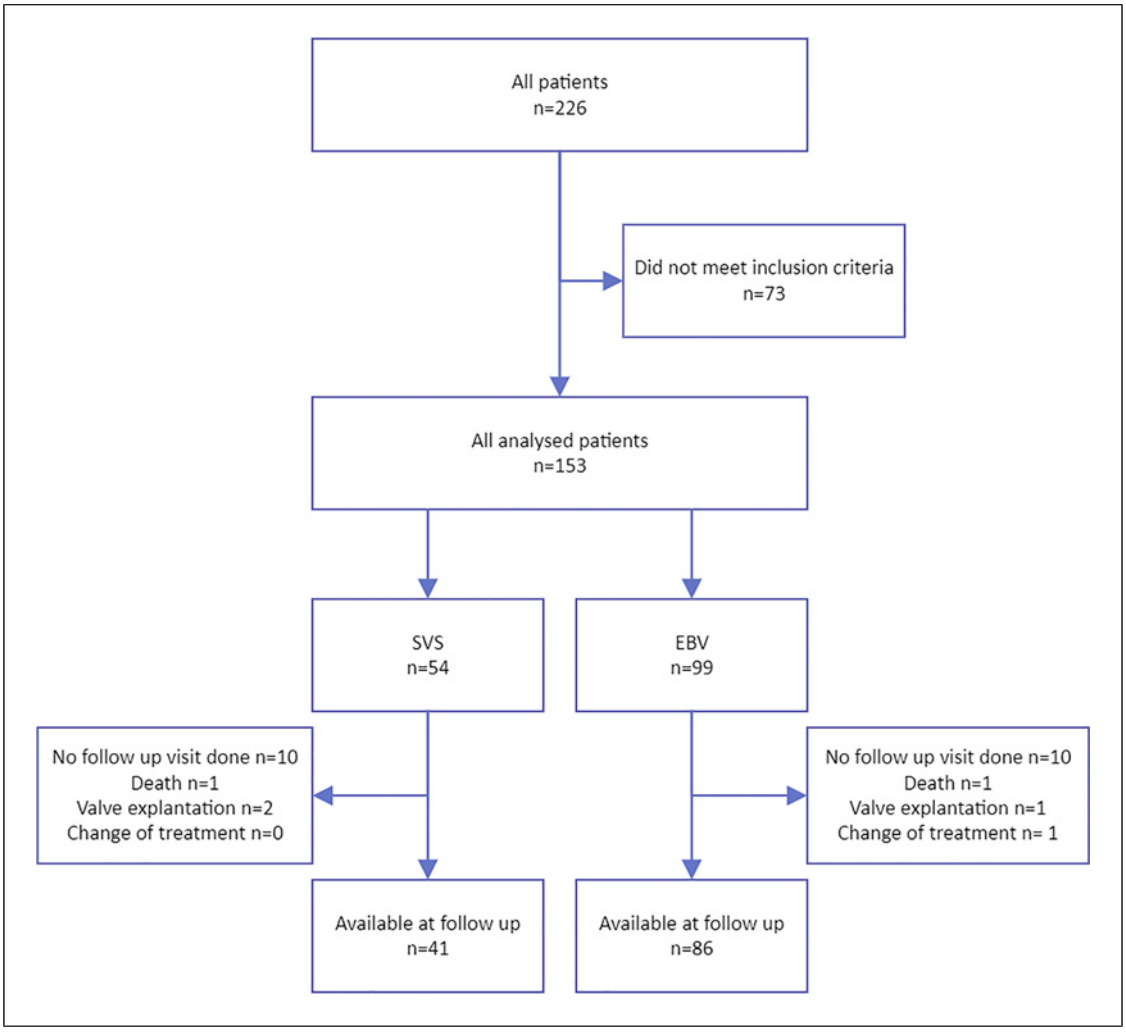

Fig. 1. Flowchart of patient selection.

procedure. A follow-up was counted as complete and included in the analysis if there were data entered for the FEV_1 and the RV at the follow-up. A flowchart of the patient selection for this study can be seen in Figure 1.

Procedures

Following parameters were assessed at baseline and at follow-up: FEV_1, diffusion capacity of the lung for carbon monoxide (DLCO), RV, pCO_2, 6MWD, CAT, mMRC, St. George's Respiratory Questionnaire (SGRQ), and adverse events. When data from the 3-month follow-up were not available for a patient, we used data from the 6-month follow-up if possible. Adverse events were assessed during the first 90 days post-intervention with one-way valves. The lung function tests including spirometry, body plethysmography, and measurement of diffusion capacity were performed according to current guidelines [24–26]. Additionally, the emphysema assessment involved high-resolution computer tomography scanning (−950 or −910 Hounsfield units) and software-based quantification (StratX platform or VIDA Diagnostics) to calculate an emphysema score. After the decision for ELVR with one-way valves was reached in the multidisciplinary conference, either the EBV or the SVS was inserted. Both valve types were always available to the physicians in all sizes. The selection of valve type was made arbitrarily by the physician performing the procedure, unless the underlying bronchial anomaly suggested a clearly superior valve type. In line with current literature, the SVS tended to be preferred in short and round bronchi, while the EBV was preferred for longer and straight bronchi [27]. All interventions were conducted according to current guidelines [28–33].

Statistical Analysis

All study data were managed using the RedCap electronic data capture tools provided by the Charité – Universitätsmedizin Berlin [34]. In this paper, continuous variables are presented as medians and interquartile ranges, while categorical variables are expressed as numbers and percentages. The median difference (Δ) was calculated using the difference between the baseline and the follow-up values in each patient before calculating the median and interquartile range for all these differences. Both the Mann-Whitney U test and the chi-square test were used to compare the baseline characteristics of both groups, depending on the type of variable tested. Wilcoxon rank test was employed for comparison of the baseline characteristics to their respective follow-up in both groups, respectively. The Mann-Whitney U test was also used to compare the median difference in lung function, exercise capacity, and quality of life between both groups. A comparison of the adverse events between both groups was performed using the chi-square test. A p value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS software, Version 27.0.0.0 (IBM Corp., Armonk, NY, USA).

Results

Baseline Characteristics

Table 1 depicts the baseline characteristics of both groups. ELVR was performed 66 times in the Gemeinschaftskrankenhaus Havelhöhe, with 50 patients receiving EBV and 16 receiving SVS. In the Charité – Universitätsmedizin Berlin, 43 patients were treated using EBV and 18 with SVS, in total 61 patients were treated. The Lungenklinik Hemer performed ELVR 26 times, with 20 patients receiving SVS and six EBV. In this study, 54 patients were treated with the SVS and 99 patients with the EBV. Both groups present with a comparable age distribution, body mass index, emphysema score, and sex ratio. The median time to follow-up did not show a significant difference between both groups. Also, comorbidities, number of valves placed, lung function, 6MWD, and quality of life did not significantly differ between both groups.

Clinical Outcome

After ELVR, a significant improvement of FEV_1 and RV was seen in both groups from baseline to follow-up (all $p < 0.001$) (Table 2). Additionally, the SGRQ and CAT score improved significantly both in the SVS and the EBV group ($p < 0.05$ for both). An increase in DLCO was observed in both groups, but this was only statistically significant in the group which received an intervention with EBV ($p < 0.05$). Similarly, the 6MWD trended towards an improvement after 3 months in both groups with only the improvement in the EBV group being significant ($p = 0.003$). Although both groups showed improvements in the mMRC score, these were only statistically significant in the group treated with the EBV ($p < 0.001$).

Table 3 depicts the median difference from baseline to the follow-up. When comparing both groups, there is no statistically significant difference in any measured parameter.

Adverse Events

There were no statistically significant differences in the rate of adverse events between both groups in the first 90 days post-intervention (Table 4). One patient (1%) died 34 days after the ELVR in the EBV group. This death was caused by an acute respiratory failure induced by the ELVR procedure. One mortality was observed in the SVS group. The cause of death in this patient could not be determined by the center treating the patient. Valves were removed in 2 patients in the SVS group (4%) and only in 1 patient in the EBV group (1%; $p = 0.284$).

The most common adverse event in both groups was pneumothorax (SVS: $n = 5/54$, 9% versus EBV: $n = 12/99$, 12%; $p = 0.601$). Other common adverse events were acute exacerbation of COPD and pneumonia. Two patients of the SVS group (4%) required mechanical ventilation, whereas none of the patients in the other group had to be ventilated ($p = 0.123$). One patient in the SVS group (2%) and 1 patient in the EBV group (1%) had to admitted to an intensive care unit (p = not applicable). Both sepsis and post-interventional bleeding occurred in the EBV group ($p > 0.05$). There was no case of severe post-interventional bleeding.

Discussion

This study aimed to assess the efficacy and safety of the two predominant types of one-way valves for ELVR. To our knowledge, this is the first study directly comparing these two valve types head-to-head. Regardless of the valve-type employed, we saw a significant improvement in FEV_1, RV, and CAT score at the follow-up. Notably, there were no significant discrepancies between the two groups regarding the median change from baseline to follow-up. Furthermore, the rate of adverse events

Table 1. Patient baseline characteristics

	SVS	EBV	*p* value
Patients, *n*	54	99	
Age, years	62.5 (11.0)	66.0 (8.0)	0.162
BMI, kg/m^2	23.8 (8.2)	26.7 (5.9)	0.206
Sex, *n* (%)			0.866
Male	29 (54)	55 (56)	
Female	25 (46)	44 (44)	
Comorbidities, *n* (%)			
α1-antitrypsin deficiency	2 (4)	3 (3)	0.620
Cardiovascular disease	5 (9)	19 (19)	0.162
Pulmonary hypertension	4 (7)	8 (8)	n.a.
Atrial fibrillation	2 (4)	4 (4)	n.a.
Arterial hypertension	21 (39)	39 (39)	0.951
Osteoporosis	2 (4)	9 (9)	0.330
Diabetes mellitus type II	4 (7)	3 (3)	0.244
Lung cancer	0 (0)	0 (0)	–
Active tumor	0 (0)	0 (0)	–
Number of valves placed	4.0 (1.0)	4.0 (2.0)	0.235
Time to follow-up, days	102.0 (35.0)	92.0 (17.0)	0.130
Emphysema score (−950 HU)[a]	42.0 (21.0)	45.0 (19.0)	0.467
Lung function test at baseline			
FEV_1, % of pred.	29.5 (13.8)	27.0 (10.0)	0.108
RV, % of pred.	237.0 (56.0)	250.0 (65.0)	0.058
DLCO, % of pred.	27.5 (14.0)	24.0 (14.3)	0.346
pCO_2, mm Hg	39.0 (6.4)	41.0 (6.6)	0.221
6MWD, m	217.0 (161.0)	247.5 (142.0)	0.485
CAT, points	28.0 (8.0)	25.5 (9.0)	0.255
mMRC, points	3.0 (2.0)	3.0 (1.0)	0.070
SGRQ, points	69.1 (19.1)	65.9 (18.6)	0.198

Data presented as median (IQR) unless indicated otherwise. Highlighted *p* value indicates statistically significant results. Mann-Whitney U test and chi-square test were used. SVS, Spiration Valve System; EBV, Zephyr endobronchial valve; BMI, body mass index; FEV_1, forced expiratory volume in 1 s; RV, residual volume; DLCO, diffusion capacity of the lung for carbon monoxide; 6MWD, 6-min walking distance; pCO_2, partial pressure of carbon dioxide; CAT, COPD Assessment Test; mMRC, Medical Research Council dyspnea; SGRQ, St. George's Respiratory Questionnaire; pred., predicted, n.a., not applicable; IQR, interquartile range. [a]Software automated quantification of emphysema destruction (−950 HU).

remained comparably low in both groups, suggesting no difference in safety profiles between both valve types.

We were able to show positive outcomes for both the SVS and EBV. The choice of valve selection was determined by the physician performing the bronchoscopy based on the unique individual bronchial anatomy of the patient. Both valve types were always available in all sizes to the treating physicians. Data from the three centers were collected using the German lung emphysema registry. This registry is a national, open-label, prospective clinical study which focusses on lung volume reduction in patients with severe emphysema. Interestingly, the baseline characteristics of both groups did not differ significantly between each other, underscoring the success of our multicenter approach in establishing two comparable cohorts.

The implantation of one-way valves was established in clinical practice following several large and high-profile RCTs [12–16, 18, 35] which successfully demonstrated efficacy and safety in the setting of a clinical trial. Other studies were able to show the feasibility and efficacy of ELVR for several different groups deemed as high risk.

Table 2. Comparison of parameters assessed from baseline to follow-up

	SVS, baseline, $n = 41$	SVS, follow-up, $n = 41$	p value	EBV, baseline, $n = 86$	EBV, follow-up, $n = 86$	p value
FEV_1, L	0.81 (0.20)	0.96 (0.32)	<**0.001**	0.72 (0.30)	0.79 (0.31)	<**0.001**
FEV_1, % of pred.	31.00 (13.50)	31.50 (20.30)	<**0.001**	27.00 (9.25)	30.00 (13.50)	<**0.001**
RV, L	5.41 (1.63)	4.72 (2.31)	**0.001**	5.84 (1.62)	4.88 (1.80)	<**0.001**
RV, % of pred.	239.00 (48.00)	205.00 (92.00)	<**0.001**	248.00 (70.00)	217.85 (62.00)	<**0.001**
DLCO, mm Hg	1.75 (2.24)	2.16 (1.04)	0.172	2.11 (1.30)	2.15 (1.64)	**0.003**
DLCO, % of pred.	27.00 (13.00)	28.00 (12.00)	0.993	24.00 (14.00)	27.00 (15.00)	**0.007**
pCO_2, mm Hg	39.25 (5.60)	37.90 (6.50)	0.130	41.00 (6.60)	39.00 (7.60)	0.086
6MWD, m	225.00 (171.00)	285.00 (165.00)	0.486	242.50 (143.00)	295.00 (120.00)	**0.003**
CAT, points	27.00 (7.00)	22.00 (8.00)	**0.009**	26.00 (11.00)	23.00 (9.00)	**0.002**
mMRC, points	3.00 (2.00)	3.0 (1.00)	0.677	3.00 (1.00)	3.00 (1.00)	<**0.001**
SGRQ, points	67.45 (18.14)	57.18 (23.25)	**0.042**	65.72 (18.66)	60.03 (24.72)	<**0.001**

Data presented as median (IQR). Highlighted p value indicates statistically significant results. Wilcoxon rank test was used. SVS, Spiration Valve System; EBV, Zephyr endobronchial valve; 3moFU, 3-month follow-up; FEV_1, forced expiratory volume in 1 s; RV, residual volume; DLCO, diffusion capacity of the lung for carbon monoxide; 6MWD, 6-min walking distance; pCO_2, partial pressure of carbon dioxide; CAT, COPD Assessment Test; mMRC, Medical Research Council dyspnea; SGRQ, St. George's Respiratory Questionnaire; pred., predicted; IQR, interquartile range.

Table 3. Changes in lung function and clinical parameters at follow-up

	SVS ($n = 41$)	EBV ($n = 86$)	p value
FEV_1, L	0.1 (0.2)	0.1 (0.3)	0.715
FEV_1, % of pred.	3.0 (8.5)	4.0 (9.0)	0.351
RV, L	−0.5 (1.3)	−0.8 (1.7)	0.517
RV, % of pred.	−24.0 (61.5)	−32.5 (74.8)	0.800
DLCO, mm Hg	0.2 (1.2)	0.3 (1.1)	0.596
DLCO, % of pred.	0.0 (14.5)	3.0 (12.5)	0.134
pCO_2, mm Hg	−0.2 (4.5)	−0.3 (5.7)	0.985
6MWD, m	20.0 (111.0)	20.0 (109.0)	0.207
CAT, points	−4.0 (11.0)	−2.0 (8.0)	0.383
mMRC, points	0.0 (1.0)	0.0 (1.0)	0.057
SGRQ, points	−9.0 (25.9)	−7.9 (15.1)	0.864

Data presented as median (IQR). Highlighted p value indicates statistically significant results. Mann-Whitney U test was used. SVS, Spiration Valve System; EBV, Zephyr endobronchial valve; FEV_1, forced expiratory volume in 1 s; RV, residual volume; DLCO, diffusion capacity of the lung for carbon monoxide; 6MWD, 6-min walking distance; pCO_2, partial pressure of carbon dioxide; CAT, COPD Assessment Test; mMRC, Medical Research Council dyspnea; SGRQ, St. George's Respiratory Questionnaire; pred., predicted; IQR, interquartile range.

For example, patients with pulmonary hypertension or a baseline FEV_1 of under 20% [19, 36]. The respective RCTs focused exclusively on one type of one-way valve, either the SVS or EBV. The EMPROVE study is one of the more recent studies using SVS in ELVR [12]. In it, Criner et al. were able to show significant improvements in FEV_1 of 99 mL and a decrease in RV of 402 mL from baseline to 6-month follow-up. Furthermore, they observed a non-significant decrease of the 6MWD of 4.4 m 6 months after the intervention with SVS. Our real-world data are consistent with these clinical trials and demonstrate comparable findings at the follow-up. Patients treated with SVS improved significantly with median ΔFEV_1 increase of 110 mL and median ΔRV decrease by 570 mL. The median Δ6MWD did improve slightly in our SVS group (6.8 m), albeit also nonsignificantly.

The LIBERATE study investigated the efficacy of EBV valves [13]. At the 12-month follow-up, they reported an increase in FEV_1 of 104 mL, a decrease in RV of 490 mL, and an improvement in the 6MWD of 13.0 m. Our findings among patients treated with EBV mirror these outcomes, revealing a significant increase in median ΔFEV_1 by 100 mL and a decrease of 820 mL in the median ΔRV at follow-up. Additionally, we observed a significant increase of 38 m in the median Δ6MWD in our EBV patients. Interestingly, DLCO improved in both groups

Table 4. Adverse events during the 3-month follow-up period

Adverse events	SVS (n = 54)	EBV (n = 99)	p value
Valve explantation, n (%)	2 (4)	1 (1)	0.284
ICU, n (%)	1 (2)	1 (1)	n.a.
Mechanical ventilation, n (%)	2 (4)	0 (0)	0.123
Death, n (%)	1 (2)	1 (1)	n.a.
Sepsis, n (%)	0 (0)	1 (1)	n.a.
Bleeding, n (%)	0 (0)	2 (2)	0.540
Pneumonia, n (%)	2 (4)	4 (4)	0.789
AECOPD, n (%)	2 (4)	5 (5)	n.a.
Pneumothorax, n (%)	5 (9)	12 (12)	0.601

Highlighted p value indicates statistically significant results. Chi-square test was used. SVS, Spiration Valve System; EBV, Zephyr endobronchial valve; ICU, intensive care unit; AECOPD, acute exacerbation of chronic obstructive pulmonal disease; n.a., not applicable.

but only significantly in the EBV group. However, this difference may be attributed to the smaller number of patients treated with SVS compared to EBV. This notion is supported by the fact that there are no significant differences between the EBV and SVS group when directly comparing their median difference from baseline to the follow-up. This suggests a comparable rate of improvement between both groups.

Furthermore, we saw a significant improvement in quality of life, measured by SGRQ, in our EBV group (−6.9 points), which is similar to those seen in the LIBERATE study at 12 months [13] (−7.6 points). Additionally, we detected a comparable significant decrease in the SGRQ of 7.1 points in the SVS patients. In both the SVS group and EBV group, we observed a significant decrease in the severity of symptoms caused by COPD, as measured by the CAT score. The mMRC score decreased in both groups, with significantly reduction only in EBV patients. Nevertheless, when comparing both groups, we found no significant differences in the degree of improvements in quality of life among them.

Both groups present with a good safety profile, seen by a low rate of severe adverse events. In the large RCTs, pneumothorax and acute exacerbation of COPD emerged as the most frequent adverse events, regardless of valve-type employed [13–15]. These two serious adverse events were also among the most common in our study and occurred at rates similar to previous clinical trials or at even lower rates [12, 13]. One of the main advantages of ELVR with one-way valves is the possibility of safely removing the valves [37]. The rate of valve explantation in this study was relatively low, with only one EBV patient (1%) and two SVS patients (4%) undergoing valve removal within in the first 90 days post-intervention. We observed one death, attributed to device-related complications. Most importantly, no significant differences were observed between the SVS and EBV groups regarding any measured adverse events, suggesting that both valve types do not significantly differ in their rate of serious adverse events.

The primary limitation of this study lies in the uneven distribution of valve types used during interventions. As the study is not a RCT, there is potential of bias in the selection of valve type by the performing physician, potentially leading to expert bias. However, the similar baseline characteristics and the multicenter approach employed in this study mitigate this bias to some extent. Still, it seems that physicians tended to prefer the EBV, most likely due to more valves being placed in longer bronchi. This would be line with other, similarly structured, papers where there also tended to be an imbalance towards the EBV [27]. To reach more conclusive conclusions, future randomized studies with more balanced groups are needed. Another limitation pertains to missing data, which is characteristic of studies of this nature. Also characteristic for studies of this type is the loss of follow-up at 3 months and beyond, this currently limits the significance and number of follow-ups available for the analysis. We saw a higher rate of loss of follow-up in the SVS group, which could skew results. Due to the nature of the registry, several interesting parameters (e.g., target lobe lung volume pre- and post-intervention, procedure

time, time of hospital stay, pO_2, target lobe volume reduction, and pulmonal arterial pressure) did not get tracked. Additionally, there is no guarantee that all serious adverse events and mortalities were consistently tracked and reported by the study centers.

Conclusion

Our study demonstrates significant improvements in lung function and disease severity across both groups. Furthermore, we observed no statistically significant differences in outcomes and safety between both groups, indicating the safety and efficacy of both valve types in the treatment of severe lung emphysema. Our study suggests that the choice of valve type does not have an impact on the outcomes. As recently suggested by Dittrich et al. [27], we also recommend SVS for short and round bronchi and EBV for longer bronchi. However, further randomized studies are needed to validate our findings.

Acknowledgments

We thank all members of the Lungenemphysemregister e.V., Grit Barten, and Laura Grebe (both CAPNETZ Lungenstiftung), Leonore Erdmann, Konrad Neumann, and Andreas Hetey (all Charité – Universitätsmedizin Berlin) for patient recruitment, data sampling, and data analysis.

Statement of Ethics

The ethic approval for the study was given by the Local Ethics Committee of Charité – Universitätsmedizin Berlin under the registration no. EA2/149/17. A written informed consent was obtained from every patient prior to the enrollment in the study.

Conflict of Interest Statement

The authors declare the following financial or nonfinancial interests which may be considered as potential conflicts of interest: Philipp Borchers: honoraria from GSK. Jacopo Saccomanno: honoraria from Pulmonx, Chiesi; travel expenses from Pulmonx, Medtronic, and AstraZeneca. Martin Witzenrath: grants from CAPNETZ STIFTUNG, BMBF (Federal Ministry of Education and Research), DFG (German Research Foundation), Biotest, Pantherna, Aptarion; honoraria from Biotest, Pantherna, Aptarion, AstraZeneca, Chiesi, Insmed, Gilead, Pfizer, Boehringer. Ralf-Harto Hübner: honoraria from Pulmonx, Olympus; Head of Lungenemphysem Register e.V.

Funding Sources

This study was not supported by any sponsor or funder.

Author Contributions

Thomas Sgarbossa did the data analysis, created the tables, and wrote the manuscript himself. Ralf-Harto Hübner and Martin Witzenrath were always available for guidance and offered feedback throughout the writing process. Katharina Ahrens was very helpful in offering many helpful corrections concerning the correct use of English and the "scientific vocabulary". The rest of the authors – Philipp Borchers, Jacopo Saccomanno, Hannah Friederike Wüstefeld, Eva Pappe, Uta Wülfing, Ulrich Klein, Franz Stanzel, and Christian Grah – were instrumental in collecting all the data used in this analysis.

Data Availability Statement

The data that support the findings of this study are not publicly available due to them containing information that could compromise the study participant privacy but are available from Thomas Sgarbossa (thomas.sgarbossa@charite.de) upon reasonable request.

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