Assessment of efficacy and safety of endoscopic lung volume reduction with one-way valves in patients with a very low FEV_1

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Abstract

Introduction Endoscopic lung volume reduction (ELVR) with one-way valves produces beneficial outcomes in patients with severe emphysema. Evidence on the efficacy remains unclear in patients with a very low forced expiratory volume in 1 s (FEV_1) (⩽20% predicted). We aim to compare clinical outcomes of ELVR, in relation to the FEV_1 restriction.

Methods All data originated from the German Lung Emphysema Registry (Lungenemphysem Register), which is a prospective multicentric observational study for patients with severe emphysema after lung volume reduction. Two groups were formed at baseline: FEV_1 ⩽20% pred and FEV_1 21–45% pred. Pulmonary function tests (FEV_1, residual volume, partial pressure of carbon dioxide), training capacity (6-min walk distance (6MWD)), quality of life (modified Medical Research Council dyspnoea scale (mMRC), COPD Assessment Test (CAT), St George's Respiratory Questionnaire (SGRQ)) and adverse events were assessed and compared at baseline and after 3 and 6 months.

Results 33 patients with FEV_1 ⩽20% pred and 265 patients with FEV_1 21–45% pred were analysed. After ELVR, an increase in FEV_1 was observed in both groups (both $p<0.001$). The mMRC and CAT scores, and 6MWD improved in both groups (all $p<0.05$). The SGRQ score improved significantly in the FEV_1 21–45% pred group, and by trend in the FEV_1 ⩽20% pred group. Pneumothorax was the most frequent complication within the first 90 days in both groups (FEV_1 ⩽20% pred: 7.7% *versus* FEV_1 21–45% pred: 22.1%; $p=0.624$). No deaths occurred in the FEV_1 ⩽20% pred group up to 6 months.

Conclusion Our study highlights the potential efficacy of one-way valves, even in patients with very low FEV_1, as these patients experienced significant improvements in FEV_1, 6MWD and quality of life. No death was reported, suggesting a good safety profile, even in these high-risk patients.

Introduction

COPD has been identified as a major public health problem and ranked third in the burden of disease and mortality in 2019 [1–4]. One of the major components of COPD is lung emphysema. In advanced stages, emphysema incurs airspace enlargement due to extensive destruction of the alveolar walls, thus resulting in severe hyperinflation and limited gas exchange [5, 6]. Inevitably, patients present with worse clinical condition, *e.g.* dyspnoea, limited exercised capacity and reduced quality of life.

To alleviate hyperinflation, lung volume reduction surgery (LVRS) has been proposed to produce favourable clinical outcomes and improve the quality of life, even in patients with severe lung emphysema [7, 8]. However, evidence from the National Emphysema Treatment Trial (NETT), the largest randomised trial to date, suggests that patients undergoing LVRS with a very low forced expiratory volume in 1 s (FEV_1) (⩽20% pred) and a very low diffusion capacity of the lung for carbon monoxide (D_{LCO}) (⩽20% pred) are still burdened by a high rate of morbidity and mortality [8], although long-term follow-up results of this subset of patients showed promising results [9–11]. Due to these findings, only few patients with a very low FEV_1 were included in subsequent studies.

At present, endoscopic lung volume reduction (ELVR) with the deployment of one-way valves (endobronchial valves) has emerged as a less invasive treatment approach alternative to surgery leading to comparable clinical outcomes [12–15]. However, patients with a very low FEV_1 did not meet inclusion criteria or were often not represented in the randomisation of their analysis [13, 16]. Evidence on patients with a very low FEV_1 comes predominantly from small case series, which are uncontrolled or underpowered to detect meaningful clinical effects [17, 18]. Therefore, it is still unknown whether endoscopic approaches with the implantation of valves might benefit patients with high frailty.

Owing the lack of robust clinical evidence, we used data from the largest prospective national registry on lung emphysema in Germany aiming to describe outcomes in patients with a very low FEV_1 undergoing ELVR with valves. To this end, we examined whether patients with a very low FEV_1 (FEV_1 ⩽20% pred) and patients with FEV_1 between 21–45% pred have similar clinical benefits and risks of adverse events.

Methods

All clinical and radiological data were extracted from the Lung Emphysema Registry (LE-Registry). The LE-Registry is a national multicentre open-label observational clinical study, which collects data exclusively on patients with severe lung emphysema undergoing lung volume reduction (https://lungenemphysemregister.de/). The focus of the registry is to compare and assess clinical outcomes after endoscopic or surgical lung volume reduction independent of any biotechnology or pharmaceutical company. The present study was approved by the local ethics committee of Charité Universitätsmedizin Berlin under the registration number EA2/149/17. Written informed consent was signed by every enrolled patient.

Inclusion and exclusion criteria

Inclusion criteria were optimised pharmacological treatment of COPD prior to intervention; proof of smoking abstinence over 3 months (cotinine levels in urine or carboxyhaemoglobin (COHb) <2%); dyspnoea primarily due to hyperinflation; participation in mobility programmes; FEV_1 ⩽45% predicted; residual volume (RV) ⩾180% pred; total lung capacity >100% pred; and 6-min walk distance (6MWD) ⩽450 m. Furthermore, collateral ventilation was assessed using Chartis (Pulmonx, Redwood City, CA, USA) and/or by software-dependent analysis of fissure integrity (StratX platform; Pulmonx or VIDA Diagnostics, Coralville, IA, USA) prior to the intervention with endobronchial valves.

Exclusion criteria were age <40 years; inability to sign a consent form; and failure to document FEV_1 levels at baseline. Individual treatment strategies were determined at each local treatment site in multidisciplinary conferences consisting of experienced pulmonologists, thoracic surgeons and radiologists.

In this specific analysis, we examined solely patients undergoing ELVR with one-way valves. These patients were split into two groups based on FEV_1 levels at baseline: group 1 (very low FEV_1: ⩽20% pred) and group 2 (low FEV_1: 21–45% pred).

Procedures

All interventions were conducted according to current guidelines [19–24]. The heterogeneity of the emphysema was assessed by calculating an emphysema score using software-based quantification of high-resolution computed tomography at −950 or −910 HU (StratX platform or VIDA Diagnostics). The emphysema was defined as homogeneous if the difference between the emphysema score of the target lobe

and ipsilateral adjacent lobe was <15% [25]. The same inclusion criteria were used for patients with either heterogeneous or homogeneous emphysema. In the absence of collateral ventilation between the lobes, the Zephyr valve system (Pulmonx) or the Spiration Valve System (Olympus, Center Valley, PA, USA) were inserted. Pulmonary function tests, such as FEV_1, RV, D_{LCO}, the 6-min walk test, the modified Medical Research Council dyspnoea scale (mMRC), the COPD Assessment Test (CAT), St George's Respiratory Questionnaire (SGRQ), as well as the occurrence of adverse events were analysed at baseline and at 3-month and 6-month follow-up. All pulmonary function tests were performed using current standards for spirometry, body plethysmography and diffusion capacity measurements [26–28].

Statistical analysis

Study data were managed by REDCap electronic data capture tools, organised by the Charité Universitätsmedizin Berlin [29]. Categorical variables are presented as numbers and percentages. Continuous variables are presented as mean±SD. Normal distribution was tested with the Shapiro–Wilk test. Baseline characteristics between both groups were compared using the Mann–Whitney U-test for continuous variables and Chi-squared test for categorical variables. The Friedman test was used to compare baseline characteristics of both groups with their respective 3- and 6-month follow-ups. The mean difference (Δ) was determined by calculating the difference between the baseline and the 3- or 6-month follow-up value in each patient before calculating the mean±SD for each of these differences. Comparisons of lung function, exercise capacity and quality-of-life data between the ΔFEV_1 groups were performed using the Mann–Whitney U-test. The Chi-squared test was used to compare adverse events between both groups. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS software (version 27.0.0.0; IBM, Armonk, NY, USA).

Results

Baseline characteristics

In this study, 33 patients with very low FEV_1 (⩽20% pred) and 265 patients with FEV_1 21–45% pred were included. Patients with FEV_1 ⩽20% pred were significantly younger (mean±SD age 61.2±7.0 years) compared to FEV_1 21–45% pred (66.6±7.2 years; p<0.001). A significant predominance of male sex was determined in the very low FEV_1 group (FEV_1 ⩽20% pred: 75.8% male *versus* FEV_1 21–45% pred: 46.8% male; p=0.007). Moreover, significant differences were observed concerning the body mass index (FEV_1 ⩽20% pred: 22.8±7.4 $kg \cdot m^{-2}$ *versus* FEV_1 21–45% pred: 25.0±7.6 $kg \cdot m^{-2}$; p=0.026), FEV_1, RV, D_{LCO}, partial pressure of carbon dioxide (P_{CO_2}) and 6MWD (p<0.01 for all). A detailed breakdown of the baseline characteristics is presented in table 1.

Clinical outcome

Tables 2 and 3 show clinical outcomes after the implantation of one-way valves at 3- and 6-month follow-up. After ELVR, both groups showed a significant increase in FEV_1 from baseline up to 6-month follow-up (p<0.001). Similarly, RV decreased significantly within 6 months in both groups (p<0.05 for both). A trend towards decrease of P_{CO_2} was observed in patients with FEV_1 ⩽20% pred at 3-month follow-up, but at the 6-month follow-up, P_{CO_2} levels returned to baseline. Correspondingly, we observed a nonsignificant increase of D_{LCO} in patients with FEV_1 ⩽20% pred at 3-month follow-up, which trended towards the baseline at the 6-month follow-up. Concerning the 6MWD, significant improvements were observed after 3- and 6-month follow-up, regardless of FEV_1 levels (p<0.02 for both). The mMRC and CAT score improved significantly across both groups when comparing the baseline and both follow-ups (p<0.05 for all). A significant improvement in the SGRQ was only observed in the FEV_1 21–45% pred group (p=0.001). Of note, only the ΔCAT score differed significantly between both FEV_1 groups at 3-month follow-up (FEV_1 ⩽20% pred: −5.1±7.4 *versus* FEV_1 21–45% pred: −2.1±6.4; p=0.038) (table 4). No significant differences were observed when comparing the mean differences between the two groups at 6-month follow-up (table 5).

Adverse events

There were no significant differences in adverse events between both groups post-intervention from zero to 3 months (table 6). Two (1.1%) patients with FEV_1 21–45% pred died during this observation period. The first patient, aged 74 years, died because of acute respiratory failure induced by ELVR. The second patient died due to a myocardial infarction, unrelated to ELVR. No deaths were seen in the FEV_1 ⩽20% pred group.

Pneumothorax was the most common complication in both groups (FEV_1 ⩽20% pred: two (7.7%) out of 26 *versus* FEV_1 21–45% pred: 42 (22.1%) out of 190; p=0.624). Acute exacerbation of COPD was more prevalent in the FEV_1 21–45% pred group (FEV_1 ⩽20% pred: two (7.7%) out of 26 *versus* FEV_1 21–45% pred: 24 (12.6%) out of 190; p=1.000). Eight (4.2%) patients with FEV_1 21–45% pred were admitted to an

TABLE 1 Baseline characteristics

	FEV_1 ⩽20% pred	FEV_1 21–45% pred	p-value
Patients	33	265	
Age years	61.24±6.96	66.59±7.22	**<0.001**
BMI kg·m^{-2}	22.76±7.40	24.96±7.66	**0.026**
Sex			**0.007**
Male	25 (75.8)	124 (46.8)	
Female	8 (24.2)	140 (52.8)	
Comorbidities			
α_1-Antitrypsin deficiency	1 (3.0)	12 (4.5)	0.771
Cardiovascular disease	5 (15.2)	48 (18.1)	0.675
Pulmonary hypertension	2 (6.1)	17 (6.4)	1.000
Atrial fibrillation	4 (12.1)	14 (5.3)	0.124
Arterial hypertension	11 (33.3)	134 (50.6)	0.062
Osteoporosis	5 (15.2)	22 (8.3)	0.196
Diabetes mellitus type II	4 (12.1)	15 (5.7)	0.145
Lung cancer	2 (6.1)	3 (1.1)	0.096
Active tumour	0 (0)	4 (1.5)	1.000
Other	10 (30)	100 (37.7)	0.404
Emphysema score in target lobe[#]	45.90±11.31	43.16±13.05	0.270
Heterogeneity index between target lobe and adjacent lobe[#]	18.59±16.52	15.52±12.33	0.593
Lung function test at baseline			
FEV_1 L	0.55±0.11	0.79±0.20	**<0.001**
FEV_1 % pred	17.87±1.95	29.90±6.10	**<0.001**
RV L	6.79±1.61	5.66±1.17	**<0.001**
RV % pred	293.82±62.89	254.29±45.74	**<0.001**
D_{LCO} mmol·min^{-1}·kPa^{-1}	1.60±0.69	2.44±1.31	**0.001**
D_{LCO} % pred	18.28±7.41	29.12±11.82	**<0.001**
P_{CO_2} mmHg	46.93±9.28	41.23±5.74	**<0.001**
6MWD m	191.30±89.81	246.84±93.65	**0.002**
CAT points	25.87±5.70	24.85±6.45	0.624
mMRC points	3.28±0.92	3.07±0.83	0.120
SGRQ points	68.58±12.78	65.64±13.32	0.363

Data are presented as n, mean±SD or n (%), unless otherwise stated. Bold type indicates statistical significance. FEV_1: forced expiratory volume in 1 s; BMI: body mass index; RV: residual volume; D_{LCO}: diffusion capacity of the lung for carbon monoxide; P_{CO_2}: partial pressure of carbon dioxide; 6MWD: 6-min walk distance; CAT: COPD Assessment Test; mMRC: modified Medical Research Council dyspnoea scale; SGRQ: St George's Respiratory Questionnaire. [#]: software automated quantification of emphysema destruction (−950 HU).

TABLE 2 Comparison from baseline to 3- and 6-month follow-up for patients with forced expiratory volume in 1 s (FEV_1) ⩽20% pred

	FEV_1 ⩽20% pred baseline	**FEV_1 ⩽20% pred 3-month follow-up**	**FEV_1 ⩽20% pred 6-month follow-up**	p-value
Patients	33	26	17	
FEV_1 L	0.55±0.11	0.76±0.42	0.65±0.15	**<0.001**
FEV_1 % pred	17.87±1.95	24.52±8.53	21.93±4.50	**<0.001**
RV L	6.79±1.61	5.91±1.62	6.10±1.23	**0.022**
RV % pred	293.82±62.89	269.46±56.82	271.18±50.10	**0.035**
D_{LCO} mmol·min^{-1}·kPa^{-1}	1.60±0.69	2.05±1.19	1.87±0.67	0.058
D_{LCO} % pred	18.28±7.41	23.43±13.21	21.58±7.80	0.148
P_{CO_2} mmHg	46.93±9.28	42.83±5.20	47.06±8.96	0.071
6MWD m	191.30±89.81	276.71±101.65	267.27±93.58	**0.014**
CAT points	25.87±5.70	21.15±5.47	24.87±5.57	**0.012**
mMRC points	3.28±0.92	2.60±0.68	2.80±1.01	**0.003**
SGRQ points	68.58±12.78	61.29±10.91	64.53±11.31	0.273

Data are presented as n or mean±SD, unless otherwise stated. Bold type indicates statistical significance. RV: residual volume; D_{LCO}: diffusion capacity of the lung for carbon monoxide; P_{CO_2}: partial pressure of carbon dioxide; 6MWD: 6-min walk distance; CAT: COPD Assessment Test; mMRC: modified Medical Research Council dyspnoea scale; SGRQ: St George's Respiratory Questionnaire.

TABLE 3 Comparison from baseline to 3- and 6-month follow-up for patients with forced expiratory volume in 1 s (FEV_1) 21–45% pred

	FEV_1 21–45% pred baseline	FEV_1 21–45% pred 3-month follow-up	FEV_1 21–45% pred 6-month follow-up	p-value
Patients	265	190	158	
FEV_1 L	0.79±0.20	0.88±0.26	0.88±0.26	**<0.001**
FEV_1 % pred	29.90±6.10	33.94±9.16	33.94±10.27	**<0.001**
RV L	5.66±1.17	5.02±1.52	5.08±1.43	**<0.001**
RV % pred	254.29±45.74	223.80±60.05	224.40±57.71	**<0.001**
D_{LCO} mmol·min^{-1}·kPa^{-1}	2.44±1.31	2.51±1.21	2.79±1.37	**0.028**
D_{LCO} % pred	29.12±11.82	31.26±12.41	31.36±13.23	0.335
P_{CO_2} mmHg	41.23±5.74	40.06±5.93	39.52±5.87	**0.002**
6MWD m	246.84±93.65	271.80±107.84	290.74±110.82	**<0.001**
CAT points	24.85±6.45	22.68±7.25	22.75±8.12	**0.002**
mMRC points	3.07±0.83	2.66±0.95	2.61±1.04	**<0.001**
SGRQ points	65.64±13.32	57.24±18.23	57.19±19.21	**0.001**

Data are presented as n or mean±SD, unless otherwise stated. Bold type indicates statistical significance. RV: residual volume; D_{LCO}: diffusion capacity of the lung for carbon monoxide; P_{CO_2}: partial pressure of carbon dioxide; 6MWD: 6-min walk distance; CAT: COPD Assessment Test; mMRC: modified Medical Research Council dyspnoea scale; SGRQ: St George's Respiratory Questionnaire.

intensive care unit (ICU), while one (3.8%) patient from the FEV_1 ⩽20% pred group was admitted to the ICU. Pneumonia occurred in 12 (6.3%) patients from the FEV_1 21–45% pred group, compared to two (7.7%) in the FEV_1 ⩽20% pred group. In the FEV_1 ⩽20% pred group, no patient experienced either post-interventional bleeding or sepsis.

During the observation period from 3 to 6 months, acute exacerbation of COPD was among the most common adverse events (FEV_1 ⩽20% pred: three (17.6%) out of 17 *versus* FEV_1 21–45% pred: seven (4.4%) out of 158; p=0.065) (table 7). Pneumonia occurred significantly more often in the FEV_1 ⩽20% pred group (FEV_1 ⩽20% pred: three (17.6%) out of 17 *versus* FEV_1 21–45% pred: two (1.3%) out of 158; p=0.011). Five (3.2%) patients from the FEV_1 21–45% pred group developed a pneumothorax, and one (0.6%) patient was admitted to an ICU. No patient from the FEV_1 ⩽20% pred group experienced either a pneumothorax or an ICU admission. There were no deaths in either group.

Discussion

We assessed efficacy and safety of ELVR with one-way valves in a prospective German patient registry. To the best of our knowledge, this is the first study specifically presenting findings on patients with a very low FEV_1 (⩽20% pred) up to 6 months after intervention. Notably, the implantation of one-way valves significantly improved FEV_1, RV and 6MWD at 6-month follow-up in patients with FEV_1 ⩽20% pred at baseline. Moreover, these findings indicate that ELVR in patients with FEV_1 ⩽20% pred presented with a reasonable safety profile, since not a single death occurred in our 33 patients. Additionally, the rates of adverse events were substantially low.

TABLE 4 Changes in lung function and clinical parameters at 3-month follow-up

	FEV_1 ⩽20% pred	FEV_1 21–45% pred	p-value
Patients	26	190	
ΔFEV_1 L	0.21±0.36	0.09±0.20	0.064
ΔRV L	−0.88±1.73	−0.66±1.26	0.685
ΔD_{LCO} mmol·min^{-1}·kPa^{-1}	0.41±1.15	0.19±0.91	0.553
ΔP_{CO_2} mmHg	−1.88±4.32	−1.03±4.67	0.314
Δ6MWD m	62.11±89.63	23.79±90.91	0.063
ΔCAT points	−5.05±7.42	−2.06±6.42	**0.038**
ΔmMRC points	−0.61±0.98	−0.38±0.96	0.134
ΔSGRQ points	−9.34±14.13	−6.75±14.10	0.361

Data are presented as n or mean±SD, unless otherwise stated. Bold type indicates statistical significance. FEV_1: forced expiratory volume in 1 s; Δ: mean difference; RV: residual volume; D_{LCO}: diffusion capacity of the lung for carbon monoxide; P_{CO_2}: partial pressure of carbon dioxide; 6MWD: 6-min walk distance; CAT: COPD Assessment Test; mMRC: modified Medical Research Council dyspnoea scale; SGRQ: St George's Respiratory Questionnaire.

TABLE 5 Changes in lung function and clinical parameters at 6-month follow-up

	FEV_1 ⩽20% pred	FEV_1 21–45% pred	p-value
Patients	17	158	
ΔFEV_1 L	0.09±0.12	0.08±0.22	0.719
ΔRV L	−0.71±1.45	−0.54±1.16	0.746
ΔD_{LCO} mmol·min^{-1}·kPa^{-1}	0.18±0.59	0.17±1.42	1.000
ΔP_{CO_2} mmHg	−0.02±6.73	−1.24±4.60	0.817
Δ6MWD m	63.86±98.57	24.91±90.48	0.346
ΔCAT points	−2.87±6.72	−2.17±6.65	0.581
ΔmMRC points	−0.71±0.99	−0.46±1.01	0.336
ΔSGRQ points	−7.34±12.37	−7.95 ±15.09	0.653

Data are presented as n or mean±SD, unless otherwise stated. FEV_1: forced expiratory volume in 1 s; Δ: mean difference; RV: residual volume; D_{LCO}: diffusion capacity of the lung for carbon monoxide; P_{CO_2}: partial pressure of carbon dioxide; 6MWD: 6-min walk distance; CAT: COPD Assessment Test; mMRC: modified Medical Research Council dyspnoea scale; SGRQ: St George's Respiratory Questionnaire.

Ever since the NETT results suggested that patients with FEV_1 ⩽20% pred and D_{LCO} ⩽20% pred are burdened by a higher risk of morbidity and mortality after LVRS [8], therapy has been guided by individual preference rather than evidence. Trudzinski *et al.* [17] pinpointed in a retrospective analysis of 20 patients with a very low FEV_1 or very low D_{LCO} after valve therapy that there was a significant increase of FEV_1 from 500 mL to 610 mL as well as a significant decrease of RV from 6.79 L to 5.70 L 3 months after the intervention. Trudzinski *et al.* [17] did not report on quality-of-life improvements. In line with these findings, we showed that among these high-risk patients FEV_1 improved significantly at 3-month follow-up from 550 mL to 760 mL. Furthermore, we found a significant decrease in RV from 6.79 L to 5.91 L. In another retrospective analysis of 20 patients on the effects of ELVR with valves in patients with a very low FEV_1, Darwiche *et al.* [18] found similar improvements of FEV_1 after 3 months' follow-up.

Current evidence on the implantation of one-way valves comes mainly from large, randomised studies [12, 13, 30–32], which demonstrated efficacy in the setting of a clinical trial. In the EMPROVE study (Spiration Valve System), after valve implantation, patients showed a significant improvement in FEV_1 of 99 mL, a decrease in RV of 402 mL and a nonsignificant reduction in the 6MWD of 4.4 m from baseline to 6-month follow-up [12]. In the TRANSFORM study (Zephyr EBV), FEV_1 increased by 140 mL, RV decreased by 660 mL and the 6MWD increased by 36.2 m 6 months after the procedure [30]. Our results, exclusively in patients with a very low FEV_1, are comparable to the findings of the studies mentioned, even though patients with a very low D_{LCO} and FEV_1 were often missing from their analyses. We were able to show that patients with FEV_1 ⩽20% pred benefitted substantially from the implantation of valves at 3-month follow-up with a mean ΔFEV_1 and Δ6MWD increasing by 210 mL and 62.1 m, respectively. Moreover, we detected a substantial decrease on average of ΔRV of 880 mL, which is higher than described in either the EMPROVE or TRANSFORM study. Similar improvements were observed in the changes from baseline up to the 6-month follow-up, with means of ΔFEV_1 increasing by 90 mL, ΔRV

TABLE 6 Adverse events during the 3-month follow-up period

	FEV_1 ⩽20% pred	FEV_1 21–45% pred	p-value
Patients	26	190	
Adverse events			
ICU	1 (3.8)	8 (4.2)	1.000
Mechanical ventilation	0 (0)	4 (2.1)	1.000
Death	0 (0)	2 (1.1)	1.000
Sepsis	0 (0)	2 (1.1)	1.000
Bleeding	0 (0)	2 (1.1)	1.000
Pneumonia	2 (7.7)	12 (6.3)	0.332
AECOPD	2 (7.7)	24 (12.6)	1.000
Pneumothorax	2 (7.7)	42 (22.1)	0.624

Data are presented as n or n (%), unless otherwise stated. FEV_1: forced expiratory volume in 1 s; ICU: intensive care unit; AECOPD: acute exacerbation of COPD.

TABLE 7 Adverse events from 3 months to 6 months post-intervention

	FEV_1 ⩽20% pred	FEV_1 21–45% pred	p-value
Patients	17	158	
Adverse events			
ICU	0 (0)	1 (0.6)	1.000
Mechanical ventilation	0 (0)	0 (0)	
Death	0 (0)	0 (0)	
Sepsis	0 (0)	0 (0)	
Bleeding	0 (0)	1 (0.6)	1.000
Pneumonia	3 (17.6)	2 (1.3)	**0.011**
AECOPD	3 (17.6)	7 (4.4)	0.065
Pneumothorax	0 (0)	5 (3.2)	1.000

Data are presented as n or n (%), unless otherwise stated. Bold type indicates statistical significance. FEV_1: forced expiratory volume in 1 s; ICU: intensive care unit; AECOPD: acute exacerbation of COPD.

decreasing by 710 mL and a Δ6MWD increase of 63.86 m (table 4). Interestingly, patients with higher FEV_1 levels experienced similar improvements in mean ΔFEV_1 (80 mL) and ΔRV (540 mL) at 6-month follow-up as the aforementioned studies. Notably, for our patients with very low FEV_1, the decrease in RV was higher than in the studies mentioned. Nevertheless, an explanation might be that outside the highly controlled conditions of randomised studies, clinical outcomes are different between participating specialised emphysema centres of the registry.

Another point of interest is the quality of life for patients with a very low FEV_1 after the implantation of one-way valves. In the EMPROVE study, patients showed a significant improvement in SGRQ of −8.1 points, mMRC of −0.6 points and CAT of −4.3 points from baseline to 6-month follow-up [12]. Similarly, the LIBERATE study showed SGRQ improvements of −7.55 points and −0.5 points for the mMRC 1 year post-procedure [13]. In our study, the quality of life improved significantly for FEV_1 ⩽20% pred patients with −0.7 points for the mMRC and −2.9 points in the CAT score. While we detected a mean decrease in the SGRQ of −7.3 points after 6 months, this decrease was not significant when comparing baseline with 3- and 6-month SGRQ. In patients with a higher FEV_1, we observed statistically significant improvements for both the SGRQ and mMRC.

A divergence at baseline of both lung function and exercise capacity at baseline is not surprising, since FEV_1 levels have repeatedly been shown to correlate with disease severity and mortality in COPD [33]. FEV_1 is a major factor in determining presence of disease, severity and response to treatment [34]. Accordingly, in the present study patients with a very low FEV_1 presented with significantly worse RV, P_{CO_2} and exercise capacity (6MWD).

In terms of positive efficacy outcomes in both groups, our findings assert that ELVR with valves seem to present with a good safety profile attributable to the absence of death and to low complication rates in patients with a very low FEV_1. In the NETT study, the mortality rates were substantially higher for patients with a very low FEV_1 undergoing LVRS [8]. In a subsequent study on long-term follow-up of high-risk patients in the NETT study, Kaplan *et al.* [9] emphasised that LVRS can result in good clinical outcomes up to 4 years follow-up, while in the first 3 years, surgical patients in the high-risk group are subject to higher complication and mortality rates. Hence, these findings fuel the ongoing debate on whether, when and how to treat those patients. In recent small retrospective studies on ELVR with valves in patients with a very low FEV_1, the development of pneumothorax was the most frequent complication [17, 18]. Pneumothorax and acute exacerbation of COPD occurred in both FEV_1 groups, at rates that are comparable to those in previous randomised clinical trials [35].

This study has certain limitations. Firstly, even in this multicentre registry, the number of patients with a very low FEV_1 is relatively small. This might be an indication towards the hesitancy of many physicians in treating these patients with a FEV_1 ⩽20% pred. Secondly, with the data originating from a registry, missing data is a characteristic limitation seen in this type of study. The significant loss to follow-up, especially for the 6-month data, has the potential to bias our results. While all participants have pledged to include all patients receiving interventional treatment, we have no way to control which patients were included in the registry. A positive selection might bias our results. There was no way to control if all serious adverse events and mortalities were announced to the registry by participation study centres; this

might bias results regarding the safety of the procedure. Significant differences in the baseline characteristic, for example the male predominance in the FEV_1 ⩽20% pred group, might limit the application of our results to patients in general. Another limitation is that we could only include those cases from the LE-Registry for which lung function parameters were available in the registry database. The average patient in the FEV_1 ⩽20% pred group is almost 6 years younger than their FEV_1 21–45% pred counterpart. This observed age difference is probably due to the selection process in each centre of the LE-Registry. Restrictive inclusion criteria might be met earlier by patients with a lower FEV_1. The overall number of cases included in this analysis is limited, and both groups were unbalanced regarding sample sizes. However, this multicentre approach was sufficient for determining the number of cases presented here.

Conclusion

Our study shows significant improvements in FEV_1, hyperinflation and exercise capacity for patients with FEV_1 ⩽20% pred up to 6 months after treatment with one-way valves. Furthermore, we observed low rates of adverse events and the absence of deaths in this group. Therefore, ELVR with valves seems to be a viable treatment option for patients with severe emphysema and a very low FEV_1.

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