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COPD

Endoscopic lung volume reduction with endobronchial valves in very low D_{LCO} patients: results from the German Registry – Lungenemphysemregister e.V.

Pavlina Lenga[1,15], Christoph Ruwwe-Glösenkamp[1,15], Christian Grah[2], Joachim Pfannschmidt[3], Jens Rückert[4], Stephan Eggeling[5], Sven Gläser[6], Bernd Schmidt[7], Paul Schneider[8], Sylke Kurz[9], Gunda Leschber[10], Andreas Gebhardt[11], Birgit Becke[12], Olaf Schega[13], Jakob Borchardt[14] and Ralf-Harto Hübner[1]

ABSTRACT

Background: Endoscopic lung volume reduction (ELVR) with valves has been suggested to be the key strategy for patients with severe emphysema and concomitant low diffusing capacity of the lung for carbon monoxide (D_{LCO}). However, robust evidence is still missing. We therefore aim to compare clinical outcomes in relation to D_{LCO} for patients treated with ELVR.

Methods: We assessed D_{LCO} at baseline and 3 months follow-up and compared pre- and postprocedural pulmonary function test, quality of life, exercise capacity and adverse events. This is a retrospective subanalysis of prospectively collected data from the German Lung Emphysema Registry.

Results: In total, 121 patients treated with ELVR were analysed. Thirty-four patients with a D_{LCO} ⩽20% and 87 patients with a D_{LCO} >20% showed similar baseline characteristics. After ELVR, there was a decrease of residual volume (both p<0.001 to baseline) in both groups, and both demonstrated better quality of life (p<0.01 to baseline). Forced expiratory volume in 1 s (FEV_1) improved significantly only in patients with a D_{LCO} >20% (p<0.001 to baseline). Exercise capacity remained almost unchanged in both groups (p=0.3). The most frequent complication for both groups was a pneumothorax (D_{LCO} ⩽20%: 17.6% *versus* D_{LCO} >20%: 16.1%; p=0.728). However, there were no significant differences in other adverse events between both groups.

Conclusions: ELVR improves lung function as well as quality of life in patients with D_{LCO} >20% and D_{LCO} ⩽20%. Adverse events did not differ between groups. Therefore, ELVR should be considered as a treatment option, even in patients with a very low D_{LCO}.

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Endoscopic lung volume reduction with endobronchial valves can be safely performed in patients with a very low diffusing capacity of the lung (D_{LCO}). Clinical effectiveness is comparable to patients with higher D_{LCO}. https://bit.ly/3cOgDK1

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This study is registered at www.drks.de with identifier number DRKS00021207. Individual deidentified patient data will be available upon reasonable request. The study protocol will be available. This will be immediately following publication. The data will be available to investigators whose proposed use of the data has been approved by an independent review committee for individual participant data meta-analysis. Proposals may be submitted up to 36 months following article publication.

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Introduction

COPD is a highly prevalent disease worldwide, currently being among the top five causes of death [1]. In advanced disease, endoscopic lung volume reduction (ELVR) using endobronchial valves (EBV) has been shown to improve lung function, quality of life and exercise capacity for a subset of patients [2–10]. This subset consists mainly of patients suffering from severe emphysema and hyperinflation [11]. Further, endobronchial valves can only be used in candidates without evidence of collateral ventilation in adjacent targeted lung lobes [12, 13].

Analysis of the National Emphysema Treatment Trial (NETT), investigating the outcome of patients with severe emphysema undergoing surgical lung volume reduction, revealed a significantly higher mortality in patients with a preoperative diffusing capacity of the lung for carbon monoxide (D_{LCO}) of 20% or less of the predicted value [14]. Subsequently, this resulted in many of the clinical trials investigating the effectiveness of EBV treatment excluding patients with a D_{LCO} of <20% of the predicted value [3, 4, 15]. However, newer evidence suggests that lung volume reduction surgery in highly selected patients with a very low D_{LCO} might be safe in experienced centres [16].

Recently, a single-centre retrospective study suggested that endobronchial valve therapy in patients with a very low D_{LCO} does not confer an increased risk of adverse events when compared with a historical control group [17]. Clinical effectiveness, however, seemed to be smaller compared to patients with a higher D_{LCO}.

To further investigate the feasibility and effectiveness of endobronchial valve therapy in patients with very low D_{LCO}, we analysed data from the Lungenemphysemregister e.V (LE- Registry), which is a non-profit multicentre observational registry following patients after lung volume reduction in Germany. We compared incidences of adverse events and measures of clinical outcomes, as well as patient characteristics in the two groups conferring either a very low D_{LCO} ⩽20% or a D_{LCO} >20%, respectively.

Methods

Study design and inclusion criteria

All clinical data for this retrospective analysis are based on pooled prospective data from the LE-Registry (https://lungenemphysemregister.de/). The LE-Registry is a national multicentre observational open-label study collecting clinical and imaging data exclusively for severe lung emphysema patients in Germany. The LE-Registry is a non-profit organisation founded by several German hospitals. Its main emphasis lies on collecting data of patient outcomes after surgical or endobronchial lung volume reduction, independent of any biotech/pharmaceutical companies. The ethics committee of the Charité Universitätsmedizin Berlin approved the collection of data (EA2/149/17). The study was registered with the German Clinical Trials Register (DRKS00021207). Each patient consented to participation. Patients were included in this specific study if they had been treated with endobronchial valves and they had documented D_{LCO} levels at baseline and 3 months follow-up. Patients were allocated into two groups: group 1: D_{LCO} ⩽20%, group 2: D_{LCO} >20%. Data were available at 3 months follow-up for 26 out of 34 (76.5%) patients with a D_{LCO} ⩽20% and for 65 out of 87 (74.7%) patients with a D_{LCO} >20%.

Measurements

Between September 2017 and February 2020 121 patients after ELVR with EBV were included in the LE-Registry at eight emphysema centres in Germany. Inclusion criteria were: a proof of nicotine restriction over 3 months (carboxyhaemoglobin (CoHb) <2% or no cotinine levels in urine), motivation to participate

Affiliations: [1]Dept of Infectious Diseases and Respiratory Medicine, Charité – Universitätsmedizin Berlin, Berlin, Germany. [2]Dept of Internal Medicine and Respiratory Medicine, Clinic Havelhöhe Berlin, Berlin, Germany. [3]Dept of Thoracic Surgery, Heckeshorn Lung Clinic, Helios Klinikum Emil von Behring, Berlin, Germany. [4]Dept of Surgery, Competence Center of Thoracic Surgery, Charité – Universitätsmedizin Berlin, Berlin, Germany. [5]Dept of Thoracic Surgery, Vivantes Netzwerk für Gesundheit, Klinikum Neukölln, Berlin, Germany. [6]Dept of Pulmonary Medicine and Infectious Diseases, Vivantes-Klinikum Neukölln, Berlin, Germany. [7]Dept of Respiratory Medicine, DRK Kliniken Berlin Mitte, Berlin, Germany. [8]Dept of Thoracic Surgery, DRK Kliniken Berlin Mitte, Berlin, Germany. [9]Dept of Respiratory Medicine, ELK Berlin Chest Hospital, Berlin, Germany. [10]Dept of Thoracic Surgery, ELK Berlin Chest Hospital, Berlin, Germany. [11]Dept of Internal Medicine and Respiratory Medicine, Helios Hospital Emil von Behring, Berlin, Germany. [12]Dept of Respiratory Medicine, Johanniter-Krankenhaus, Treuenbrietzen, Germany. [13]Dept of Thoracic Surgery, Johanniter-Krankenhaus, Treuenbrietzen, Germany. [14]Dept of Pulmonary Medicine and Infectious Diseases, Vivantes-Klinikum Friedrichshain, Berlin, Germany. [15]These authors contributed equally.

Correspondence: Christoph Ruwwe-Glösenkamp, Dept of Infectious Diseases and Respiratory Medicine, Charité – Universitätsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin, Germany.
E-mail: christoph.ruwwe-gloesenkamp@charite.de

in a patient mobility programme, a clinical assessment that dyspnoea was caused primarily by hyperinflation, 6-min walk distance (6MWD) <450 m, forced expiratory volume in 1 s (FEV_1) <45% of predicted, residual volume (RV) >180% of predicted, total lung capacity (TLC) >100% of predicted, and absence of collateral ventilation in the target lobe assessed by Chartis® (Pulmonx, Redwood City, CA, USA) and/or by software-dependent analysis of fissure integrity (StratX platform; Pulmonx or VIDA Diagnostics, Coralville, IA, USA). Exclusion criteria were: inability to sign a consent form, significant pulmonary arterial pressure (sPAP >50 mmHg) or the omission of documentation of the D_{LCO} levels. This occurred in 15 cases. For all patients, final treatment strategies were determined in a local steering committee at each treatment site, consisting of members of the respective emphysema centres.

Procedures

All bronchoscopic procedures were conducted according to guidelines [18–21]. The emphysema score was evaluated by software-based quantification of emphysema destruction at −950 Hounsfield units (StratX platform or VIDA Diagnostics). Homogeneous emphysema was defined as <15% difference in emphysema score between target and ipsilateral adjacent lobes [3, 22]. In the absence of collateral ventilation, 73.6% Zephyr® valve system (Pulmonx) and 26.4% Spiration valve system (Olympus, USA) were implanted. Patients were evaluated at baseline and 3 months follow-up for pulmonary function tests (FEV_1, RV, TLC, D_{LCO}), clinical condition (6MWD), quality of life (St. George's Respiratory Questionnaire (SGRQ)), Medical Research Council dyspnoea scale (mMRC) and for adverse events after ELVR.

Spirometry, body plethysmography and measurement of diffusion capacity were performed according to current standards [23–25]. Normal values for D_{LCO} were taken from the European Respiratory Society (ERS) formulas [26].

Patients were considered responders if the FEV_1, RV, 6MWD, mMRC and SGRQ improved more than the minimal clinical important difference (MCID) after the implantation of endobronchial valves. We used the following MCID: improvement of FEV_1 of at least 10%, reduction of RV ⩽0.43 L, increase of 6MWD of at least 26 m, reduction of mMRC of at least 1 point and reduction of SGRQ of at least 4 points as previously described [27–31].

Statistical analysis

The Mann–Whitney U-test or Chi-squared test were used for comparison of the baseline characteristic data and the occurrence of adverse events between the D_{LCO} groups. The Chi-squared test was performed for the comparison of the MCID between D_{LCO} groups. The Mann–Whitney U-test was also performed for the comparison of lung function and quality of life data between the "delta" (Δ) D_{LCO} groups. Delta was defined as the mean difference between the D_{LCO} group at baseline and at 3 months follow-up. Since all variables were normally distributed as examined with the Shapiro–Wilk test, all parameters are presented as means with standard deviation (SD). The relation between D_{LCO} and the improvement of FEV_1 at 3 months was tested by using the Pearson correlation. To investigate associations, we used linear regression analysis models with ΔFEV_1 as the dependent variable and D_{LCO} levels as independent variables. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS software, Version 24.0.0.0 (IBM Corp., Armonk, NY, USA).

Results

Patients' baseline characteristics

We included 34 patients with D_{LCO} ⩽20% and 87 patients with D_{LCO} >20% (table 1). The mean age was 65.5±6.8 years in the D_{LCO} <20% and 64.4±15.2 years in the D_{LCO} >20% groups (p=0.69). There was a predominance of female sex in the D_{LCO} ⩽20% (58.8%) group compared to D_{LCO} >20% (37.2%; p=0.03). There was a significant difference between the groups in D_{LCO} at baseline (D_{LCO} ⩽20%: 16.1±3.4 *versus* D_{LCO} >20%: 34.7±11.8; p<0.001). Regarding the emphysema score, no significant differences were found between the groups (D_{LCO} ⩽20%: 42.9±13.3 *versus* D_{LCO} >20%: 45.8±10.7; p<0.31). No other significant differences between the groups were observed either for baseline data or for lung function, exercise capacity or the quality of life at baseline.

Clinical outcome in relation to D_{LCO} after ELVR

After ELVR, only patients with D_{LCO} ⩽20% showed a significant increase in D_{LCO} from baseline to 3 months follow-up (16.1±3.4 to 22.0±5.7, p=0.003, table 2), while patients with D_{LCO} >20% remained almost unchanged (34.7±11.8 to 34.9±12.2, p=0.75). RV decreased significantly at 3 months follow-up from baseline in both groups (p=0.01 both to baseline). There was a similar increase in FEV_1 from baseline to 3 months follow-up in both patient groups, which was only significant for patients with a D_{LCO} >20%. Both groups showed a significant improvement in quality of life at 3 months follow-up, as measured with mMRC and SGRQ compared to baseline measurements (p<0.05 for all assessments to

TABLE 1 Baseline characteristics

	D_{LCO} ⩽20% pred	D_{LCO} >20% pred	p-value
Subjects n	34	87	
Age years	65.5±6.8	64.4±15.2	0.69
BMI kg·m^{-2}	25.46±9.8	24.62±9.8	0.81
Sex %			**0.03**
Male	41.2	62.8	
Female	58.8	37.2	
Comorbidities %			
α_1-antitrypsin-deficiency	5.9	3.5	0.15
Cardiovascular disease	26.5	18.6	0.34
Pulmonary hypertension	8.8	9.3	0.94
Atrial fibrillation	5.9	8.1	0.67
Arterial hypertension	35.3	55.8	**0.04**
Osteoporosis	5.9	9.3	0.54
Diabetes mellitus type II	2.9	4.7	0.67
Lung cancer	0.0	1.2	0.17
Active tumours	0.0	2.3	0.53
Others	20.6	26.7	0.77
Emphysema score in target lobe[#]	42.9±13.3	45.8±10.7	0.31
Heterogeneity index between target and adjacent lobe[#]	22.7±9.6	21.0±12.5	0.45
Lung function test at baseline			
FEV_1 % pred	30.0±9.5	33.0±9.9	0.11
RV % pred	261.1±49.6	251.4±52.3	0.51
D_{LCO} % pred	16.1±3.4	34.7±11.8	**<0.001**
6MWD m	254.7±92.8	276.6±115.9	0.94
mMRC points	3.4±0.7	3.0±0.9	0.25
SGRQ points	60.7±12.0	59.6±11.9	0.98

Data are presented as mean±SD unless otherwise stated. D_{LCO}: diffusing capacity of the lung for carbon monoxide; BMI: body mass index; FEV_1: forced expiratory volume in 1 s; RV: residual volume; 6MWD: 6-min walk distance; mMRC: Medical Research Council dyspnoea; SGRQ: St George's Respiratory Questionnaire. [#]: software automated quantification of emphysema destruction (−950 Hounsfield units). Bold indicates statistical significance.

baseline). The 6MWD slightly increased at 3 months follow-up, irrespective of D_{LCO}, but was not statistically different compared to baseline (p=0.15). At 3 months follow-up there were no differences in the lung function parameters (FEV_1 and RV, exercise capacity (6MWD) or in quality of life (mMRC, SGRQ)) between both D_{LCO} groups. D_{LCO} in patients with an initially low D_{LCO} improved significantly, unlike in patients with higher D_{LCO} rates at 3 months follow-up (table 3).

TABLE 2 Comparison between diffusing capacity of the lung for carbon monoxide (D_{LCO}) groups from baseline to 3 months follow-up

	D_{LCO} ⩽20% pred			**D_{LCO} >20% pred**		
	Baseline	**3-month follow-up**	**p-value**	**Baseline**	**3-month follow-up**	**p-value**
Subjects n	34	26		87	65	
D_{LCO} % pred	16.1±3.4	22.0±5.7	**0.003**	34.7±11.8	34.9±12.2	0.75
FEV_1 L	0.8±0.3	0.9±0.4	0.09	0.9±0.3	1.01±0.1	**0.001**
FEV_1 % pred	30.0±9.5	33.3±9.8	0.08	33.0±9.9	36.84±12.0	**0.001**
RV L	5.9±1.1	5.5±1.7	**0.01**	5.6±1.9	4.93±1.4	**0.01**
RV % pred	261.1±49.6	246.0±73.3	**0.01**	251.4±52.3	211.51±52.0	**<0.001**
6MWD m	254.7±92.8	305.4±117.2	0.15	276.6±115.9	296.00±128.2	0.15
mMRC points	3.4±0.7	3.0±0.8	**0.02**	3.0±0.9	2.72±1.0	**0.03**
SGRQ points	60.7±12.0	50.0±17.7	**0.049**	59.6±11.9	53.78±14.8	**0.04**

Data are presented as mean±SD unless otherwise stated. FEV_1: forced expiratory volume in 1 s; RV: residual volume; 6MWD: 6-min walk distance; mMRC: Medical Research Council dyspnoea; SGRQ: St George's Respiratory Questionnaire. Bold indicates statistical significance.

TABLE 3 Change in lung function and clinical parameters at 3 months follow-up

	D_{LCO} ⩽20% pred	D_{LCO} >20% pred	p-value
Subjects n	26	65	
ΔD_{LCO} kPa	0.35±0.86	0.03±1.10	0.04
ΔFEV_1 L	0.17±0.42	0.11±0.25	0.70
ΔRV L	−0.5±0.9	−0.7±1.7	0.94
Δ6MWD m	38.2±88.7	31.3±109.7	0.30
ΔmMRC points	−0.5±1.7	−0.4±0.9	0.83
ΔSGRQ points	−12.4±16.4	−6.0±11.5	0.29

Data are presented as mean±SD unless otherwise stated. D_{LCO}: diffusing capacity of the lung for carbon monoxide; FEV_1: forced expiratory volume in 1 s; RV: residual volume; 6MWD: 6-min walk distance; mMRC: Medical Research Council dyspnoea; SGRQ: St George's Respiratory Questionnaire.

Table 4 depicts the responders achieving an MCID in outcome measures. There were no significant differences in outcomes between patients with a D_{LCO} ⩽20% and those with a D_{LCO} >20%.

There was no significant correlation between D_{LCO} levels and ΔFEV_1 (Pearson's R=−0.008; p=0.939, data not shown). After performing regression analysis models, there was no association between D_{LCO} and ΔFEV_1 at 3 months of follow-up (B=−0.04; p=0.678, data not shown).

Adverse events

There were no significant differences in complication rates between both groups (table 5). The most common complication was pneumothorax (D_{LCO} ⩽20%: 23.1% *versus* D_{LCO} >20%: 21.5%; p=0.73). An acute exacerbation of COPD occurred in one patient (3.8%) in the D_{LCO} ⩽20% group and in 13 patients (14.9%) in the D_{LCO} >20% group (p=0.07). In both cohorts, no deaths occurred until the 3-month follow-up. Three patients with a D_{LCO} >20% (4.6%) had to be admitted to an intensive care unit, compared to one patient in the D_{LCO} <20% group (3.8%). In the group with a D_{LCO} >20% three patients (4.6%) required mechanical ventilation. Postinterventional bleeding was present in one patient (1.5%), and pneumonia occurred in two patients (3.1%) compared to none in the group with a D_{LCO} ⩽20%.

Discussion

Patients with a very low D_{LCO} played only a marginal role in previous prospective studies on treatment outcomes after EBV [3, 4, 15]. To our knowledge, we are the first to describe outcome results for patients undergoing treatment with endobronchial valves exclusively based on a large national cohort. One of the main results indicates that ELVR for patients with a very low D_{LCO} might be a safe therapy, since complication rates were substantially low and not a single death occurred in either group. Furthermore, we found a significant amelioration of quality of life as measured with the SGRQ and of lung function in patients with a very low D_{LCO}.

Hyperinflation of the lungs as a consequence of emphysema greatly diminishes exercise capacity [32]. In addition to inhaled bronchodilators, which are the current mainstay of treatment, only lung volume

TABLE 4 Comparison of minimal clinically important difference (MCID) for forced expiratory volume in 1 s (FEV_1), residual volume (RV), 6-min walk distance (6MWD) and St George's Respiratory Questionnaire (SGRQ)

	D_{LCO} ⩽20% pred	D_{LCO} >20% pred	p-value
Subjects n	26	65	
FEV_1 L, MCID ⩾+10%	7 (26.9)	13 (20.0)	0.744
RV L, MCID ⩽−0.43 L	15 (57.7)	32 (49.2)	0.466
6MWD m, MCID ⩾+26 m	14 (53.8)	26 (40.0)	0.620
mMRC points, MCID ⩽−1 point	11 (42.3)	14 (21.5)	0.151
SGRQ points, MCID ⩽−4 points	10 (38.5)	19 (29.2)	0.795

Data are presented as n (%) unless otherwise stated. D_{LCO}: diffusing capacity of the lung for carbon monoxide; mMRC: Medical Research Council dyspnoea.

TABLE 5 Adverse events after endobronchial implantation of valves in 3 months follow-up

Adverse event	D_{LCO} ⩽20% pred	D_{LCO} >20% pred	p-value
Subjects n	26	65	
ICU	1 (3.8)	3 (4.6)	0.93
Mechanical ventilation	0.0	3 (4.6)	0.28
Death	0	0	
Sepsis	0	0	
Bleeding	0.0	1 (1.5)	0.54
Pneumonia	0.0	2 (3.1)	0.39
AECOPD	1 (3.8)	13 (20.0)	0.07
Pneumothorax	6 (23.1)	14 (21.5)	0.73

Data are presented as n (%) unless otherwise stated. D_{LCO}: diffusion capacity of the lung for carbon monoxide; ICU: intensive care unit; AECOPD: acute exacerbation of chronic obstructive pulmonary disease.

reduction, either as a surgical or endobronchial technique, is available as an established treatment option to address hyperinflation in advanced COPD [33–37]. In the largest trial to date, examining the safety and effectiveness of surgical lung volume reduction, the NETT, subgroup analysis showed an increased mortality for patients undergoing surgery with a D_{LCO} of <20% of predicted [14]. This led to several trials examining the application of endobronchial valves to exclude patients with a very low D_{LCO} from treatment [3, 4, 15].

Little is known about safety and efficacy regarding implantation of valves in patients with very low D_{LCO}. While earlier data suggest the feasibility in patients with a very low FEV_1 (<20% predicted) [38, 39], it is not known yet whether the same is true for a very low D_{LCO}.

Data collected for the current study show no statistically significant difference in outcomes for patients treated with EBV based on their D_{LCO} (tables 2 and 3). Both the >20% and ⩽20% D_{LCO} group, after EBV treatment, showed similar improvements of RV, decreased dyspnoea (mMRC) and increased life quality (SGRQ), while the 6MWD did not change significantly in either group, even though a trend towards improvement could be observed. FEV_1 increased significantly only in the >20% D_{LCO} group, potentially caused by the lower number of patients included in the very low D_{LCO} group, thus reducing statistical power. Nevertheless, we did find that only patients with very low D_{LCO} showed a significant increase in D_{LCO} after ELVR at 3 months follow-up (table 3). This might seem surprising at first glance, since lung volume reduction per definition reduces the overall alveolar surface of a lung and therefore potentially aggravates an already low diffusing capacity. However, diffusing capacity in severe lung emphysema is determined through a combination of factors including, as already mentioned, decreased alveolar surface. Additionally, diffusing capacity causes changes in the pulmonary vasculature and, most significantly, ventilation–perfusion mismatches [40, 41]. Treatment with endobronchial valves decreases ventilation–perfusion mismatches in the lung, as shown with dual energy computed tomography of the lung, thus counteracting decreases in alveolar surface [42].

Table 1 shows an important strength of the study, namely that both groups were similar in most baseline characteristics, except for sex and rate of arterial hypertension. This may seem somewhat surprising, since D_{LCO} has been shown to correlate with several parameters of COPD severity, including FEV_1 and lung density [43]. Thus, we would expect patients with a more severe disease phenotype at baseline in the very low D_{LCO} group. While a trend in terms of more severe emphysema, as measured with computed tomography quantification, and more hyperinflation, as measured with RV, can be observed, this is not statistically significant. One of the reasons for the relative homogeneity of the two groups at baseline is certainly the already highly selective process of choosing COPD patients for ELVR. All patients within the LE-Registry must fulfil restrictive criteria in terms of their baseline characteristics before being considered potential candidates for an intervention. Within this subset of patients with very severe emphysema, D_{LCO} might be perhaps less meaningful as an indicator of severity compared to milder forms of COPD.

In terms of efficacy, our data show similarly positive results as those published in previous prospective clinical trials [44]. In the LIBERATE study, the treatment group had a median reduction of RV of 490 mL, in the EMPROVE study RV reduction was 402 mL, while in our study there was a mean reduction of 540 mL in the very low D_{LCO} group, and 730 mL in the >20% D_{LCO} group [4, 9]. 6MWD increased by 38 m and 31 m, respectively, as compared to 13 m in the LIBERATE study and −4 m in the EMPROVE study, albeit there being no statistically significant difference between baseline and follow-up in our study.

This indicates reassuringly that outside of highly controlled conditions of randomised clinical trials, outcomes are similar in participating hospitals of the LE-Registry.

In addition to the positive efficacy outcomes in both D_{LCO} groups, the second main message of this study is that EBV treatment is safe even in patients with a very low D_{LCO}. There was not a single death in either group, in contrast to the results of the NETT trial, where patients with a very low D_{LCO} undergoing surgery were prone to adverse events and exhibited higher mortality rates [14].

Table 5 shows adverse events occurring during or after treatment in both groups. Reassuringly, adverse events did not differ significantly between the two groups and were overall low. Even though our study had presumably more severely ill patients by including those with a D_{LCO} <20%, rates of adverse events were not higher than those published in randomised controlled trials [44].

One of the main strengths of our study is the data originating from a multicentre, industry-independent registry. However, some limitations do exist. The included cohort of very low D_{LCO} patients is relatively small, even in this multicentre effort, potentially reflecting the hesitancy of physicians to treat patients with a very low D_{LCO} with EBV therapy. It is possible that the results of our current study will lead to more frequent treatment inclusions of this subgroup in the future. Another limitation of our study is that our recruited patients with a very D_{LCO} generally had D_{LCO} levels between 10% and 20%, and much less often below 10%, which might underpower our effect size. Since patients with a D_{LCO} of <20% played only a marginal role in general in previously published studies, we believe that our findings could still be a meaningful tool in the decision-making process of clinicians.

Furthermore, our results showed improvements in the MCID for FEV_1, RV, 6MWT and SGRQ at 3 months follow-up in both patient groups. However, these findings were partly lower than in randomised clinical trials. Perhaps a relatively high dropout rate of a quarter of patients during follow-up prevented more meaningful results in this regard. Since this is a registry, missing data are frequently inherent with this type of study. We strongly believe that there is a substantial need for further randomised trials expanding the evidence of that topic.

Conclusion

There were significant improvements in hyperinflation, dyspnoea and quality of life in patients with a very low D_{LCO}. Additionally, we observed low complication rates and absence of mortality in both groups after EBV therapy. These findings stress the importance of when discussing treatment modalities for patients with a very low D_{LCO}, the implantation of valves should be considered, since it seems to be a safe and efficacious treatment tool. These findings might serve as a basis for the development of future research focusing on the clinical outcomes of patients with a very low D_{LCO} after ELVR.

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