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

Pavlina Lenga¹,¹⁵, Christoph Ruwwe-Glösenkamp¹,¹⁵, Christian Grah², Joachim Pfannschmidt³, Jens Rückert⁴, Stephan Eggeling⁵, Sven Gläser⁶, Bernd Schmidt⁷, Paul Schneider⁸, Sylke Kurz⁹, Gunda Leschber¹⁰, Andreas Gebhardt¹¹, Birgit Becke¹², Olaf Schega¹³, Jakob Borchardt¹⁴ and Ralf-Harto Hübner¹

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 $D_{LCO} \leq 20\%$ 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 ($D_{LCO} \leq 20\%$: 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 $D_{LCO} \leq 20\%$. Adverse events did not differ between groups. Therefore, ELVR should be considered as a treatment option, even in patients with a very low $D_{LCO}$.

@ERSpublications

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

Cite this article as: Lenga P, Ruwwe-Glösenkamp C, Grah C, et al. Endoscopic lung volume reduction with endobronchial valves in very low $D_{LCO}$ patients: results from the German Registry – Lungenemphysemregister e.V. ERJ Open Res 2021; 7: 00449-2020 [https://doi.org/10.1183/23120541.00449-2020].

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.

Received: 30 June 2020 | Accepted after revision: 23 Sept 2020

Copyright ©ERS 2021. This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial Licence 4.0.
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 (DLCO) 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 DLCO 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 DLCO might be safe in experienced centres [16].

Recently, a single-centre retrospective study suggested that endobronchial valve therapy in patients with a very low DLCO 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 DLCO.

To further investigate the feasibility and effectiveness of endobronchial valve therapy in patients with very low DLCO, 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 conferred either a very low DLCO <20% or a DLCO >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 DLCO levels at baseline and 3 months follow-up. Patients were allocated into two groups: group 1: DLCO <20%, group 2: DLCO >20%. Data were available at 3 months follow-up for 26 out of 34 (76.5%) patients with a DLCO <20% and for 65 out of 87 (74.7%) patients with a DLCO >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 in the study if they had been treated with endobronchial valves and they had documented DLCO levels at baseline and 3 months follow-up. Patients were allocated into two groups: group 1: DLCO <20%, group 2: DLCO >20%. Data were available at 3 months follow-up for 26 out of 34 (76.5%) patients with a DLCO <20% and for 65 out of 87 (74.7%) patients with a DLCO >20%.

Affiliations: 1Dept of Infectious Diseases and Respiratory Medicine, Charité – Universitätsmedizin Berlin, Berlin, Germany. 2Dept of Internal Medicine and Respiratory Medicine, Clinic Hawelhöhe Berlin, Berlin, Germany. 3Dept of Thoracic Surgery, Heckeshorn Lung Clinic, Helios Klinikum Emil von Behring, Berlin, Germany. 4Dept of Surgery, Competence Center of Thoracic Surgery, Charité – Universitätsmedizin Berlin, Berlin, Germany. 5Dept of Thoracic Surgery, Heckeshorn Lung Clinic, Helios Klinikum Emil von Behring, Berlin, Germany. 6Dept of Surgery, Competence Center of Thoracic Surgery, Charité – Universitätsmedizin Berlin, Berlin, Germany. 7Dept of Thoracic Surgery, Heckeshorn Lung Clinic, Helios Klinikum Emil von Behring, Berlin, Germany. 8Dept of Thoracic Surgery, Heckeshorn Lung Clinic, Helios Klinikum Emil von Behring, Berlin, Germany. 9Dept of Thoracic Surgery, ELK Berlin Chest Hospital, Berlin, Germany. 10Dept of Thoracic Surgery, ELK Berlin Chest Hospital, Berlin, Germany. 11Dept of Internal Medicine and Respiratory Medicine, Helios Hospital Emil von Behring, Berlin, Germany. 12Dept of Thoracic Surgery, Johanniter-Krankenhaus, Treuenbrietzen, Germany. 13Dept of Thoracic Surgery, Johanniter-Krankenhaus, Treuenbrietzen, Germany. 14Dept of Pulmonary Medicine and Infectious Diseases, Vivantes-Klinikum Friedrichshain, Berlin, Germany. 15These 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-gloeenkamp@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 (FEV1) <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 ΔLCO 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 (FEV1, RV, TLC, DLCO), 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 DLCO were taken from the European Respiratory Society (ERS) formulas [26].

Patients were considered responders if the FEV1, 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 FEV1 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 DLCO groups. The Chi-squared test was performed for the comparison of the MCID between DLCO groups. The Mann–Whitney U-test was also performed for the comparison of lung function and quality of life data between the “delta” (Δ) DLCO groups. Delta was defined as the mean difference between the DLCO 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 DLCO and the improvement of FEV1 at 3 months was tested by using the Pearson correlation. To investigate associations, we used linear regression analysis models with ∆FEV1 as the dependent variable and DLCO 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 DLCO ≤20% and 87 patients with DLCO >20% (table 1). The mean age was 65.5±6.8 years in the DLCO <20% and 64.4±15.2 years in the DLCO >20% groups (p=0.69). There was a predominance of female sex in the DLCO ≤20% (58.8%) group compared to DLCO >20% (37.2%; p=0.03). There was a significant difference between the groups in DLCO at baseline (DLCO ≤20%: 16.1±3.4 versus DLCO >20%: 34.7±11.8; p<0.001). Regarding the emphysema score, no significant differences were found between the groups (DLCO ≤20%: 42.9±13.3 versus DLCO >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 DLCO after ELVR**

After ELVR, only patients with DLCO ≤20% showed a significant increase in DLCO from baseline to 3 months follow-up (16.1±3.4 to 22.0±5.7; p=0.003, table 2), while patients with DLCO >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 FEV1 from baseline to 3 months follow-up in both patient groups, which was only significant for patients with a DLCO >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
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 (FEV1 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 1 Baseline characteristics

| Subjects n | $D_{LCO} \leq 20\%$ pred | $D_{LCO} > 20\%$ pred | p-value |
|------------|---------------------------|------------------------|---------|
| Age years  | 65.5±6.8                  | 64.4±15.2              | 0.69    |
| BMI kg·m$^{-2}$ | 25.4±9.8              | 24.6±9.8              | 0.81    |
| Sex %      |                           |                        | 0.03    |
| Male       | 41.2                      | 62.8                   |         |
| Female     | 58.8                      | 37.2                   |         |
| Comorbidities % |                |                        |         |
| α1-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±12.3              | 0.45    |
| Lung function test at baseline |                   |                        |         |
| FEV1 % pred | 30.0±9.5              | 33.0±9.9               | 0.11    |
| RV % pred | 261.1±94.6              | 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              | 276.4±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; FEV1: 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.

### 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 | 3-month follow-up | p-value | $D_{LCO}$ > 20% pred | 3-month follow-up | p-value |
|----------------------|-------------------|---------|----------------------|-------------------|---------|
| Subjects n           | 34                | 26      | 0.003                | 87                | 65      | 0.75 |
| $D_{LCO}$ % pred     | 16.1±3.4          | 22.0±5.7| 0.01                 |                   |         |
| FEV1 L               | 0.8±0.3           | 0.9±0.4 | 0.90                 |                   |         |
| FEV1 % pred          | 30.0±9.5          | 33.3±9.8| 0.01                 |                   |         |
| RV L                 | 5.9±1.1           | 5.5±1.7 | 0.01                 |                   |         |
| RV % pred            | 261.1±94.6        | 246.0±73.3| 0.01                |                   |         |
| 6MWD m               | 254.7±92.8        | 305.4±117.2| 0.15               |                   |         |
| mMRC points          | 3.4±0.7           | 3.0±0.8 | 0.02                 |                   |         |
| SGRQ points          | 60.7±12.0         | 50.0±17.7| 0.049               |                   |         |

Data are presented as mean±SD unless otherwise stated. FEV1: 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 4 depicts the responders achieving an MCID in outcome measures. There were no significant differences in outcomes between patients with a $D_{LCO} \leq 20\%$ and those with a $D_{LCO} >20\%$.

There was no significant correlation between $D_{LCO}$ levels and $\Delta FEV_1$ (Pearson’s $r=-0.008; p=0.939$, data not shown). After performing regression analysis models, there was no association between $D_{LCO}$ and $\Delta FEV_1$ 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 ($D_{LCO} \leq 20\%$: 23.1% versus $D_{LCO} >20\%$: 21.5%; $p=0.73$). An acute exacerbation of COPD occurred in one patient (3.8%) in the $D_{LCO} \leq 20\%$ 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 $D_{LCO} \leq 20\%$ 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 $D_{LCO} \leq 20\%$.

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 $D_{LCO} \leq 20\%$ 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...
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 FEV1 (<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. FEV1 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 FEV1 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.

| 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.
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 meaningful tool in the decision-making process of clinicians. 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.

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 expanding the clinical outcomes of patients with a very low D_{LCO} after ELVR.

Conflict of interest: P. Lenga has nothing to disclose. C. Ruuwe-Grölsenkamp has nothing to disclose. C. Grah has nothing to disclose. J. Pannschmidt has nothing to disclose. J. Rücker has nothing to disclose. S. Eggeling has nothing to disclose. S. Gläser reports personal fees from Boehringer Ingelheim, grants and personal fees from Novartis Pharma, and personal fees from Roche Pharma, Berlin Chemie, PneumRx, PulmonX, Actelion Pharma and Bayer Healthcare, outside the submitted work. B. Schmidt has nothing to disclose. S. Kurz has nothing to disclose. G. Lechber has nothing to disclose. A. Gebhardt has nothing to disclose. B. Becker has nothing to disclose. O. Schega has nothing to disclose. J. Borchardt has nothing to disclose. R.-H. Hübner reports personal fees and nonfinancial support from PulmonX outside the submitted work.

References

1. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012; 380: 2095–2128.
2. Davie C, Zoumout Z, Jordan S, et al. Bronchoscopic lung volume reduction with endobronchial valves for patients with heterogeneous emphysema and intact interlobar fissures (the BeLieVeR-HiFi study): a randomised controlled trial. Lancet 2015; 386: 1066–1073.
3. Sciuara FC, Ernst A, Herth FJ, et al. A randomized study of endobronchial valves for advanced emphysema. N Engl J Med 2010; 363: 1233–1244.
4. Criner GJ, Sue R, Wright S, et al. A multicenter randomized controlled trial of Zephyr endobronchial valve treatment in heterogeneous emphysema (LIBERATE). Am J Respir Crit Care Med 2018; 198: 1151–1164.
5. Klooster K, ten Hacken NH, Hartman JE, et al. Endobronchial valves for emphysema without interlobar collateral ventilation. N Engl J Med 2015; 373: 2325–2335.
6. Valipour A, Siebos DJ, Herth F, et al. Endobronchial valve therapy in patients with homogeneous emphysema. Results from the IMPACT Study. Am J Respir Crit Care Med 2016; 194: 1073–1082.
7. Kemp SV, Siebos DJ, Kirk A, et al. A multicenter randomized controlled trial of Zephyr endobronchial valve treatment in heterogeneous emphysema (TRANSFORM). Am J Respir Crit Care Med 2017; 196: 1535–1543.
8. Li S, Wang G, Wang C, et al. The REACH Trial: a randomized controlled trial assessing the safety and effectiveness of the Spiratory valve system in the treatment of severe emphysema. Respir Res 2019; 97: 416–427.
Lee SW, Lee SM, Shin SY, Yamaguchi K, Mori M, Kawai A, Criner GJ, Eberhardt R, Fernandez-Bussy S, van Dijk M, Hartman JE, Klooster K, Peinado VI, Pizarro S, Barberà JA. Pulmonary vascular involvement in COPD. Ann Thorac Surg 2005; 79: 411–416.

Caviezel C, Schaffter N, Schneiter D, Koster TD, van Rikxoort EM, Huebner RH, et al. Interventional bronchoscopy: state-of-the-art review. Am J Respir Crit Care Med 2020; 202: 29–50.

Garner JL, Shah PL. Lung volume reduction in pulmonary emphysema. Semin Respir Crit Care Med 2020; 41: 874–885.

Shah PL, Slebos D-J. Bronchoscopic interventions for severe emphysema: where are we now? Respirology 2020; 25: 972–980.

Valipour A, Shah PL, Gesierich W, et al. Patterns of emphysema heterogeneity. Respitation 2015; 90: 402–411.

Criée CP, Baur X, Berdel D, Aalstad LT, Hardie JA, Espehaug B, et al. [Standardization of spirometry: 2015 update. Published by German Atemwegsliga, German Respiratory Society and German Society of Occupational and Environmental Medicine]. Pneumologie 2015; 69: 147–164.

Wanger J, Clausen JL, Coates A, et al. Standardisation of the measurement of lung volumes. Eur Respir J 2005; 26: 511–522.

Macintyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J 2005; 26: 720–735.

Cotes JE, Chinn DJ, Quanjer PH, et al. Standardization of the measurement of transfer factor (diffusing capacity). Eur Respir J 1993; 6: Suppl. 16, 41–52.

Donohue JP. Minimal clinically important differences in COPD lung function. COPD 2005; 2: 111–124.

Hartman JE, Ten Hacken NH, Klooster K, et al. The minimal important difference for residual volume in patients with severe emphysema. Eur Respir J 2012; 40: 1137–1141.

Puhan MA, Chandra D, Mosenifar Z, et al. The minimal important difference of exercise tests in severe COPD. Eur Respir J 2011; 37: 784–790.

Jones PW. St. George’s Respiratory Questionnaire: MCID. COPD 2005; 2: 75–79.

Welling JB, Hartman JE, Ten Hacken NH, et al. The minimal important difference for the St George’s Respiratory Questionnaire in patients with severe COPD. Eur Respir J 2015; 46: 1598–1604.

Aalstad LT, Hardie JA, Espenhau B, et al. Lung hyperinflation and functional exercise capacity in patients with COPD – a three-year longitudinal study. BMC Pulm Med 2018; 18: 187.

Singh D, Agusti A, Anzueto A, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease; the GOLD science committee report 2019. Eur Respir J 2019; 53: 1900164.

Hartman JE, Vanfleteren LEGW, van Rikxoort EM, et al. Endobronchial valves for severe emphysema. Eur Respir Rev 2019; 28: 180121.

Ruwwe-Glösenkamp C, Döllinger F, Suttorp N, et al. Endoskopische Emphysemtherapie. Der Pneumologe 2020; 17: 12–21.

Shah PL, Herth FJ, van Geffen WH, et al. Lung volume reduction for emphysema. Lancet Respir Med 2017; 5: 147–156.

Klooster K, Hartman JE, Ten Hacken NHT, et al. Improved predictors of survival after endobronchial valve treatment in patients with severe emphysema. Am J Respir Crit Care Med 2017; 195: 1272–1274.

Trudzinski FC, Höink AJ, Leppert D, et al. Endoscopic lung volume reduction using endobronchial valves in patients with severe emphysema and very low FEV1. Respiratio 2016; 92: 258–265.

Darwich K, Karpf-Wissel R, Eisenmann S, et al. Bronchoscopic Lung Volume Reduction with Endobronchial Valves in Low-FEV1 Patients. Respiration 2016; 92: 414–419.

Peinado VI, Pizarro S, Barberá JA. Pulmonary vascular involvement in COPD. Chest 2008; 134: 808–814.

Yamaguchi K, Mori M, Kawai A, et al. Inhomogeneities of ventilation and the diffusing capacity to perfusion in various chronic lung diseases. Am J Respir Crit Care Med 1997; 156: 86–93.

Lee SW, Lee SM, Shin SY, et al. Improvement in ventilation-perfusion mismatch after bronchoscopic lung volume reduction: quantitative image analysis. Radiology 2017; 285: 250–260.

Gould GA, Redpath AT, Ryan M, et al. Lung CT density correlates with measurements of airflow limitation and the diffusing capacity. Eur Respir J 1991; 4: 141–146.

van Geffen WH, Slebos D-J, Herth FJ, et al. Surgical and endoscopic interventions that reduce lung volume for emphysema: a systemic review and meta-analysis. Lancet Respir Med 2019; 7: 313–324.