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Original article

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Endoscopic lung volume reduction with endobronchial valves in very low DLCO patients: results from the German Registry (Lungenemphysemregister e.V.)

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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 diffusion capacity of the lung for carbon monoxide (DLCO). However, robust evidence is still missing. We therefore aim to compare clinical outcomes in relation to DLCO for patients treated with ELVR.

Methods

We assessed DLCO at baseline and 3-months follow-up and compared pre- and postprocedural pulmonary function test (PFT), quality of life, exercise capacity and adverse events. This is a retrospective subanalysis of prospectively collected data from the German Lung Emphysema Registry.

Results

121 patients treated with ELVR were analysed. 34 patients with a DLCO ≤20% and 87 patients with a DLCO >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 1s (FEV1) improved significantly only in patients with a DLCO >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 (DLCO ≤20%: 17.6% vs DLCO >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 DLCO >20% and DLCO ≤20%. Adverse events did not differ between groups. Therefore, ELVR should be considered as a treatment option, even in patients with a very low DLCO.

Introduction

Chronic obstructive pulmonary disease (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 (DLCO) of 20% or less of the predicted value [14]. Subsequently, this caused many of the clinical trials investigating the effectiveness of EBV treatment to exclude patients with a DLCO of less than 20% of the predicted value [3, 15, 16]. However, newer evidence suggests that lung-volume-reduction surgery in highly selected patients with a very low DLCO might be safe in experienced centers [17].

Recently, a single-center 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 [18]. 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 analyzed data from the Lungenemphysemregister e.V (LE-Registry), which is a non-profit multicenter observational registry following patients after lung volume reduction in Germany. We compared incidences of adverse events, measures of clinical outcomes, as well as patient characteristics in the two groups conferring a very low DLCO $\leq$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 multicenter observational open-label study collecting clinical and imaging data exclusively for severe lung emphysema patients in Germany. The LE-Registry is a non-profit organization, founded by several German hospitals. Its main emphasis lies on collecting data of patient outcomes after surgical or endobronchial lung volume reduction, independent from 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 into this specific study if they were 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%. Available data on 3-months-follow-up were for 26/34 (76.5%) patients with a DLCO≤20% and for 65/87 (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 centers in Germany. Inclusion criteria were: a proof of nicotine restriction over 3 months (CoHb <2% or no Cotinine levels in urine), motivation to participate in a patient mobility program, a clinical assessment that dyspnea was caused primarily by hyperinflation, 6-minutes walking distance (6-MWD) <450m, forced expiratory volume in 1s (FEV1) <45% of predicted, residual volume (RV) >180% of predicted, total lung capacity (TLC) > 100% of predicted, absence of collateral ventilation in the target lobe assessed by Chartis® (Pulmonx, USA) and/ or by software dependent analysis of fissure integrity (StratX,platform, PulmonX, USA or Vida Diagnostics, USA). Exclusion criteria were: inability to sign a consent form, significant pulmonary hypertension (sPAP >50mmHg), or the omission of documentation of the DCLO 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 centers.

Procedures

All bronchoscopic procedures were conducted according to guidelines [19-22]. The emphysema score was evaluated by software based quantification of emphysema destruction at -950 hounsfield unit (StratX platform or VIDA Diagnostics). Homogeneous emphysema was defined as less than 15% emphysema difference in emphysema score between target and ipsilateral adjacent lobes [3, 23]. In absence of collateral ventilation 73.6% Zephyr® valve system (Pulmonx, USA) 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 (6-MWD), quality of life (St. George's Respiratory Questionnaire (SGRQ), medical research council dyspnea scale (MMRC), and for adverse events after ELVR.

Spirometry, body plethysmography and measurement of diffusion capacity were performed according to current standards [24-26]. Normal values for DLCO were taken from the European respiratory Society (ERS) formulas [27].

Patients were considered responders if the FEV1, RV, 6-MWD, mMRC and SRGQ 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 equal or less than 0.43 L, increase of 6-MWD of at least 26 m, reduction of mMRC of at least 1 point and reduction of SGRQ of at least 4 point as previously described [28-32].

Statistical analysis

The Mann-Whitney-U-test or chi-square test were used for the comparison of the baseline characteristic data and the occurrence of adverse events between the DCLO groups. The chi-square 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 DCLO 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 three months was tested by using the Pearson correlation. To investigate associations, we used linear regression analysis models with ΔFEV1 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% (p=0.69). There was a predominance of female gender in the DLCO≤20% (58.8%) compared to DLCO>20% (37.2%; p=0.03). There was a significant difference between both groups in DLCO at baseline (DLCO≤20%: 16.1± 3.4vs 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 vs DLCO >20%: 45.8± 10.7; p<0.31). No other significant differences between both 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 of DLCO from baseline to 3-months follow-up (16.1±3.4 to 22.0±5.7, p=0.003, table2), 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 at 3-months follow-up 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 baseline). The 6-MWD slightly increased at 3-months follow-up, irrespective of DLCO, but 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 (6-MWD) or in quality of life (mMRC, SGRQ) between both DLCO groups with a DLCO ≤20% and with a DLCO >20%. DLCO in patients with an initially low DLCO improved significantly, unlike in patients with higher DLCO rates at 3-months follow-up (table 3).

Table 4 depicts the responders achieving an MCID in outcome measures. There were no significant differences in outcomes between patients with a DLCO ≤20% and those with a DLCO> 20%.

There was no significant correlation between DLCO levels and ΔFEV1 (Pearson's R=-0.008; p=0.939, data not shown). After performing regression analysis models, there was no association between DLCO and ΔFEV1 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 (DLCO ≤20%: 23.1% versus DLCO >20%: 21.5%; p=0.73). An acute exacerbation of COPD occurred in one patient (3.8%) in DLCO ≤20% and in 13 patients (14.9%) in DLCO >20% (p=0.07). In both cohorts, no deaths occurred until the 3-months follow-up. Three patients with a DCLO >20% (4.6%) had to be admitted to an ICU, compared to one patient in the DLCO <20% group (3.8%). In the group with a DLCO >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 DLCO≤20%.

Discussion

Patients with a very low-DLCO played only a marginal role in previous prospective studies on treatment outcomes after EBV [3, 15, 16]. 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 DLCO 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 DLCO.

Hyperinflation of the lungs as a consequence of emphysema greatly diminishes exercise capacity [33]. 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 [34-38]. In the largest trial to date, examining the safety and effectiveness of surgical lung volume reduction, the National Emphysema Treatment Trial (NETT), subgroup analysis showed an increased mortality for patients undergoing surgery with a DLCO of less than 20% of predicted [14]. This led several trials examining the application of endobronchial valves to exclude patients with a very low DLCO from treatment [3, 15, 16].

Little is known about safety and efficacy regarding implantation of valves in patients with very low DLCO. While earlier data suggest the feasibility in patients with a very low FEV1 (<20% predicted) [39, 40], it is not known yet, if the same is true for a very low DLCO.

Data collected for the current study show no statistically significant difference in outcomes for patients treated with EBV based on their DLCO (Table 2 and 3). Both, the >20% and ≤20% DLCO-group, after EBV-treatment, showed similar improvements of RV, decreased dyspnea (mMRC) and increased life quality (SGRQ), while the 6-MWD did not change significantly in either group, even though a trend towards improvement could be observed. FEV1 increased significantly only in the >20% DLCO group, potentially caused by the lower number of patients included in the very low DLCO group, thus reducing statistical power. Nevertheless, we did find that only patients with very low DLCO showed a significant increase of DLCO 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 [41, 42]. 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 [43].

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 DCLO has been shown to correlate with several parameters of COPD severity, including FEV1 and lung density [44]. Thus, we would expect patients with a more severe disease phenotype at baseline in the very low DLCO group. While a trend in terms of more severe emphysema, as measured with CT-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 fulfill 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, DLCO 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 [45]. In the LIBERATE study, the treatment group had a median reduction of RV of 490ml, in the EMPROVE study RV reduction was 402ml, while in our study there was a mean reduction of 540ml in the very low DLCO group, and 730ml in the >20% DLCO group [4, 9]. 6-MWD increased by 38m and 31m respectively, as compared to 13m in the LIBERATE study and -4m 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 randomized clinical trials, outcomes are similar in participating hospitals of the LE-Registry.

In addition to the positive efficacy outcomes in both DLCO groups, the second main message of this study is that EBV treatment is safe even in patients with a very low DLCO. There was not a single death in either group, in contrast to the results of the NETT trial, where patients with a very low DLCO 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 DLCO <20%, rates of adverse events were not higher than those published in randomized controlled trials [45].

One of the main strengths of our study is the data originating from a multicenter, industry independent registry. However, some limitations do exist. The included cohort of very low DLCO patients is relatively small, even in this multicenter effort, potentially reflecting the hesitancy of physicians to treat patients with a very low DLCO with EBV therapy. Maybe the results of our current study 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 DLCO had mainly DLCO levels between 10% and 20%, and much less often below 10%, which might underpower our effect size. Since patients with a DLCO of less than 20% played only a marginal role in general in previous 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 for the MCID for FEV1, RV, 6MWT and SGRQ at 3-months follow up in both patient groups. However, these findings were partly lower than in randomized 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 randomized trials expanding the evidence of that topic.

Conclusion

There were significant improvements in hyperinflation, dyspnea and quality of life in patients with a very low DLCO. Additionally, we observed low complication rates and absence of mortality in both groups after EBV therapy. These findings stress the importance, that when discussing treatment modalities for patients with a very low DLCO, the implantation of valves should be considered, since it seems to be a safe and an 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 DCLO after ELVR.

Table 1: Baseline characteristics

	DLCO≤20% (n=34)	**DLCO>20% (n=87)**	**p**
Age (y)	65.5 (6.8)	64.4 (15.2)	0.69
BMI (kg/m2)	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-antithrypsin-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 melitus type II	2.9	4.7	0.67
Lung cancer	0.0	1.2	0.17
Active tumors	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			
FEV1, % pred.	30.0 (9.5)	33.0 (9.9)	0.11
RV, % pred.	261.1 (49.6)	251.4 (52.3)	0.51
DLCO, %pred.	16.1 (3.4)	34.7 (11.8)	**<0.001**
6-MWD (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

Abbreviations: Diffusion capacity of the lung for carbon monoxide (DLCO), Body Mass Index (BMI), forced expiratory volume in 1s (FEV1), Residual volume (RV), 6-min walking distance (6-MWD), Medical Research Council dyspnea (mMRC), St. George's Respiratory Questionnaire (SGRQ). Predicted (pred.) Data represented as mean ± SD unless otherwise specified. *Software automated quantification of emphysema destruction (-950HU)

Table 2: Comparison between DLCO groups from baseline to 3-months follow-up

	DLCO≤20% Baseline n=34	**DLCO≤20% 3mo FU n=26**	**p**	**DLCO>20% Baseline n=87**	**DLCO>20% 3mo FU n=65**	**p**
DLCO, % pred.	16.1 (3.4)	22.0 (5.7)	**0.003**	34.7 (11.8)	34.9 (12.2)	0.75
FEV1, L	0.8 (0.3)	0.9 (0.4)	0.09	0.9 (0.3)	1.01 (0.1)	**0.001**
FEV1, % 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**
6-MWD (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**

Abbreviations: Diffusion capacity of the lung for carbon monoxide (DLCO), 3-months follow-up (3mo FU), forced expiratory volume in 1s (FEV1), Residual volume (RV), 6-min walking distance (6-MWD), Medical Research Council dyspnea (mMRC), St. George's Respiratory Questionnaire (SGRQ), predicted (pred.), meters (m). Data represented as mean (SD).

Table 3: Delta of lung function and clinical parameter at 3-months follow-up
Abbreviations: Diffusion capacity of the lung for carbon monoxide (DLCO), Forced expiratory volume in 1s (FEV1), Residual volume (RV), 6-min walking distance (6-MWD), Medical Research Council dyspnea (mMRC), St. George's Respiratory Questionnaire (SGRQ). Data represented as mean (SD).

	DLCO≤20% n=26	**DLCO>20% n=65**	**p**
ΔDLCO (kPa)	0.35 (0.86)	0.03 (1.10)	0.04
ΔFEV1 (L)	0.17 (0.42)	0.11 (0.25)	0.70
ΔRV (L)	-0.5 (0.9)	-0.7 (1.7)	0.94
Δ6-MWD (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

Table 4: Comparison of MCID for FEV1, RV, 6MWD, SGRQ.

	DLCO≤20% n=26	**DLCO>20% n=65**	**p**
FEV1 (L), MCID ≥+10%	7 (26.9%)	13 (20.0%)	0.744
RV (L), MCID≤-0.43L	15 (57.7%)	32 (49.2%)	0.466
6-MWD (m), MCID≥+26m	14 (53.8%)	26 (40.0%)	0.620
mMRC (points), MCID ≤-1point	11 (42.3%)	14 (21.5%)	0.151
SGRQ (points), MCID ≤-4 points	10 (38.5%)	19 (29.2%)	0.795

Abbreviations: Minimal clinically important difference (MCID), Diffusion capacity of the lung for carbon monoxide (DLCO), Forced expiratory volume in 1s (FEV1), Residual volume (RV), 6-min walking distance (6-MWD), Medical Research Council dyspnea (mMRC), St. George's Respiratory Questionnaire (SGRQ).

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

Adverse events	**DLCO≤20% n=26**	**DLCO>20% n=65**	**p**
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

Abbreviations: Diffusion capacity of the lung for carbon monoxide (DLCO), intensive care unit (ICU); acute exacerbation of chronic obstructive pulmonal disease (AECOPD). Data represented as mean (SD).

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