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Endoscopic Lung Volume Reduction with One-Way Valves in Patients with Severe Chronic Obstructive Pulmonary Disease with Hypercapnia

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Keywords
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Abstract
Background: Robust clinical evidence on the efficacy and safety of endoscopic lung volume reduction (ELVR) with one-way valves in patients with severe lung emphysema with chronic hypercapnic respiratory failure is lacking. ***Objective:*** The aim of this study was to compare patient characteristics, clinical outcome measures, and incidences of adverse events between patients with severe COPD undergoing ELVR with one-way valves and with either a partial pressure of carbon dioxide (pCO_2) of ≤45 mm Hg or with pCO_2 >45 mm Hg. ***Methods:*** This was a multicentre prospective study of patients with severe lung disease who were evaluated based on lung function, exercise capacity (6-min walk test [6-MWT]), and quality-of-life tests. ***Results:*** Patients with pCO_2 ≤45 mm Hg (n = 157) and pCO_2 >45 mm Hg (n = 40) showed similar baseline characteristics. Patients with pCO_2 ≤45 mm Hg demonstrated a significant increase in forced expiratory volume in 1 s ($p < 0.001$), a significant decrease in residual volume (RV) ($p < 0.001$), and significant im-

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provements in the quality of life and 6-MWT at the 3-month follow-up. Patients with pCO_2 >45 mm Hg had significant improvements in RV only ($p < 0.05$). There was a significant decrease in pCO_2 between baseline and follow-up in hypercapnic patients, relative to the decrease in patients with pCO_2 ≤45 mm Hg ($p = 0.008$). Patients who were more hypercapnic at baseline showed a greater reduction in pCO_2 after valve placement ($r = -0.38$, $p < 0.001$). Pneumothorax was the most common adverse event in both groups. ***Conclusions:*** ELVR with one-way valves seems clinically beneficial with a remarkably good safety profile for patients with chronic hypercapnic respiratory failure.

Introduction

Chronic obstructive pulmonary disease (COPD) is a debilitating disease that is currently ranked fourth worldwide in terms of disease burden and mortality [1, 2]. Chronic cigarette smoking induces an inflammatory occlusion of the small airway. Consequently, an increase of hyperinflation and emphysematous remodelling of the lung parenchyma results in reduced gas-exchange surface area and elastic recoil. All these factors contribute to a worse clinical condition, causing dyspnoea, limited exercise capacity, and reduced quality of life. In the advanced stages of the disease, the sustained increase in residual volume (RV) and concurrent respiratory muscle dysfunction can lead to hypoxic and hypercapnic respiratory failure [3, 4].

Previous studies on lung volume reduction surgery (LVRS) suggested that this procedure might be beneficial and lead to favourable outcomes even in patients with hypercapnia [5, 6]. In contrast, the National Emphysema Treatment Trial (NETT), the largest randomized trial to date, reported that hypercapnic patients are associated with an increased risk of mortality after LVRS [7]. Another retrospective monocentric study correlated partial pressure of carbon dioxide (pCO_2) levels >45 mm Hg with a worse outcome and longer hospitalization after surgery [8]. These findings led subsequent studies to preclude these patients from their study.

Implantation of one-way valves leads to a deflation of lung emphysema with partial amelioration of breathing mechanics. Recent studies have demonstrated significant improvements in lung function parameters, exercise capacity, and quality of life, with an overall reasonable safety profile with the Zephyr® valve system (Pulmonx, Redwood City, CA, USA) (10–13) or the Spiration Valve System (Olympus, Center Valley, PA, USA) [9, 10]. Nevertheless, a mandatory criterion for endoscopic lung volume reduction (ELVR) is pCO_2 <45–50 mm Hg. Available data on patients with pCO_2 >45 mm Hg come from small retrospective studies on the implantation of endobronchial coils or valves that have been either uncontrolled or underpowered to detect meaningful clinical effects [11–13]. As such, these findings are still inconclusive, and a subject of debate is whether one-way valve implantation is a safe and efficient treatment approach for patients with significant hypercapnia.

Based on the knowledge that there are no studies available comparing the suitability and outcomes of normocapnic and hypercapnic patients undergoing valve implantation and in the context that these patients have been considered at higher risk for the occurrence of adverse events or even death, we asked whether patients with hypercapnia (pCO_2 >45 mm Hg) may benefit from ELVR. Using data from the largest comprehensive nationwide registry of patients with severe emphysema in Germany, we compared the patient characteristics, incidences of adverse events, and measures of clinical outcomes between groups of COPD patients with either pCO_2 ≤45 mm Hg or pCO_2 >45 mm Hg.

Materials and Methods

Study Design

All data were derived from the Lungenemphysem Register e.V. (LE-Registry) (www.lungenemhysemregister.de), which is a national multicentre prospective open-label clinical study that exclusively collected data on patients with severe lung disease. The main goal of the LE-Registry was to compare outcomes after endoscopic or surgical lung volume reduction, independent of any biotechnology or pharmaceutical company. The study was approved by the Review Board of the Charité Universitätsmedizin Berlin and registered with the German Clinical Trials Registry (DRKS00021207). Each patient consented to participate in the study. The prerequisites for the eligibility of the patients for this study were as follows: (1) proof of nicotine restriction for over 3 months (carboxyhaemoglobin <2.0% or no cotinine in urine), (2) motivation to participate or current participation in a patient mobility programme, and (3) a clinical assessment showing that dyspnoea was caused primarily by hyperinflation. Patients who met the following criteria were treated with one-way valves: 6-min walk test (6-MWT) result <450 m, forced expiratory volume in 1 s (FEV1) <45% of the predicted value, RV >180% of the predicted value, total lung capacity >100% of the predicted value, and the absence of collateral ventilation in the target lobe assessed by Chartis® (PulmonX) and/or by software-dependent analysis of fissure integrity (StratX, PulmonX, or Vida Diagnostics, Coralville, IA, USA). A cut-off value of fissure integrity was not defined by study protocol since it depended on the automated software quantification systems. The decision to use an endoscopic approach with

Table 1. Summary of patient and lung emphysema characteristics

	pCO_2 ≤45 mm Hg* (*n* = 157)	pCO_2 >45 mm Hg** (*n* = 40)	*p* value
Age, years	65.5 (7.6)	64.0 (8.3)	0.422
BMI, kg/m^2	24.1 (8.9)	27.7 (11.2)	0.269
Sex, %			
Male	88 (55.1)	21 (52.5)	0.821
Female	69 (43.9)	19 (47.5)	
Comorbidities			
α_1-Antitrypsin deficiency	6 (3.8)	2 (5.0)	0.582
Cardiovascular disease	28 (17.8)	14 (35.0)	**0.018**
Pulmonary hypertension	15 (9.6)	1 (2.5)	0.145
Atrial fibrillation	11 (7.0)	3 (7.5)	0.914
Arterial hypertension	74 (47.1)	16 (40.0)	0.419
Osteoporosis	12 (7.6)	4 (10.0)	0.626
Diabetes mellitus type II	5 (3.2)	5 (12.5)	**0.017**
Lung cancer	4 (2.5)	0 (0.0)	0.308
Active tumours	2 (1.3)	1 (2.5)	0.572
Others	53 (33.8)	10 (25.0)	0.289
Echocardiography, %	125 (79.6)	31 (77.5)	0.890
Previous lung volume reduction treatment, %	15 (9.6)	3 (7.5)	0.919
Mean emphysema score in the target lobe	43.4 (14.2)	41.0 (17.8)	0.264
Lung function parameters			
FEV1, %	31.6 (9.5)	29.6 (10.4)	**0.001**
RV, %	249.8 (52.5)	271.9 (60.1)	**0.001**
DLCO, %	28.2 (11.6)	26.4 (9.7)	0.067
pCO_2, mm Hg	38.4 (3.7)	52.2 (6.2)	**<0.001**
6-MWT, m	274.8 (104.4)	236.0 (99.7)	0.066
mMRC (points)	2.9 (0.9)	3.0 (1.0)	0.137
CAT (points)	24.8 (6.7)	25.6 (6.1)	0.518
SGRQ (points)	57.4 (15.9)	62.6 (10.2)	0.100

Data are represented as mean (SD) unless otherwise specified. The highlighted *p* values indicate statistically significant results. BMI, body mass index; FEV1, forced expiratory volume in 1 s; RV, residual volume; DLCO, diffusion capacity of the lung for carbon monoxide; pCO2, partial pressure of carbon dioxide; 6-MWT, 6-min walking test; mMRC, modified Medical Research Council; CAT, COPD assessment test; SGRQ, St. George's Respiratory Questionnaire. * pCO_2 (min: 29.0 mm Hg, max: 45.0 mm Hg). ** pCO_2 (min: 45.1 mm Hg, max: 80.0 mm Hg).

valves was determined in a local steering conference committee at each treatment site, aiming to find out the best therapeutic approach for every patient.

Participant Population and Inclusion Criteria

Between September 2017 and October 2020, 197 patients undergoing ELVR with valves were included from eight centres for this specific analysis. The inclusion criteria for this sub-analysis were as follows: (1) ELVR with valves and (2) documented pCO_2 at baseline. Patients were allocated into two groups based on their pCO_2 values: group 1 (pCO_2 ≤45 mm Hg) and group 2 (pCO_2 >45 mm Hg) [3]. A detailed medical history and demographic data were extracted from the registry database and evaluated retrospectively. There was no information available on the use of non-invasive mechanical ventilation due to the study design.

Procedures

In all participating centres, patients with severe emphysema were thoroughly evaluated by the multidisciplinary emphysema board considering lung volume reduction approaches. Pulmonary function tests (FEV1, RV, diffusion capacity of carbon monoxide [DLCO]), 6-MWT, the modified Medical Research Council (mMRC) dyspnoea scale, the COPD assessment test (CAT), St. George's Respiratory Questionnaire (SGRQ), and adverse events after ELVR were evaluated at baseline and 3-month follow-up to assess the efficacy and safety of the procedure. All bronchoscopic procedures were performed according to pre-existing guidelines [14–17]. Pulmonary function tests, including spirometry, body plethysmography, measurement of diffusion capacity, and blood gas analysis, were performed according to international standards [18–20]. pCO_2 was assessed by capillary blood gas analysis as previously described [21]. Zavorsky et al. [22] described in a meta-analysis on arterial and capillary blood gases that both earlobe and

Table 2. Comparisons from baseline to the 3-month follow-up

	pCO_2 ≤45 mm Hg (n = 157)	pCO_2 ≤45 mm Hg 3 mo FU (n = 130)	p value	pCO_2 >45 mm Hg (n = 40)	pCO_2 >45 mm Hg 3 mo FU (n = 29)	p value
pCO_2, mm Hg	38.4 (3.7)	37.3 (3.7)	0.418	52.2 (6.2)	43.7 (8.6)	**0.008**
FEV1, L	0.87 (0.3)	0.99 (0.3)	**<0.001**	0.75 (0.2)	0.83 (0.3)	0.253
FEV1, %	31.6 (9.5)	36.6 (10.1)	**<0.001**	29.6 (10.4)	33.5 (14.4)	0.253
RV, L	5.6 (1.3)	4.8 (1.5)	**<0.001**	6.1 (1.3)	5.7 (1.3)	**0.053**
RV, %	249.8 (52.5)	213.5 (58.7)	**<0.001**	271.9 (60.1)	215.0 (75.4)	**0.032**
DLCO, mm Hg	2.5 (1.4)	2.2 (1.3)	0.073	1.9 (1.0)	2.0 (0.7)	0.142
DLCO, %	28.2 (11.6)	29.8 (14.7)	0.055	23.6 (9.5)	26.4 (9.7)	0.187
6-MWT, m	274.8 (104.4)	326.6 (102.9)	**0.037**	236.0 (99.7)	269.6 (110.7)	0.435
mMRC (points)	2.9 (0.9)	2.5 (0.9)	**0.004**	3.0 (1.0)	2.8 (1.2)	0.131
CAT (points)	24.8 (6.7)	22.5 (7.0)	**0.004**	25.6 (6.1)	23.8 (7.0)	0.190
SGRQ (points)	57.4 (15.9)	55.0 (16.4)	**0.028**	62.6 (10.2)	60.4 (15.7)	0.500

Data represented as mean ± SD. 3 mo FU, 3-month follow-up; FEV1, forced expiratory volume in 1 s; RV, residual volume; DLCO, diffusion capacity of the lung for carbon monoxide; pCO_2, partial pressure of carbon dioxide; 6-MWT, 6-min walking test; mMRC, modified Medical Research Council; CAT, COPD assessment test; SGRQ, St. George's Respiratory Questionnaire. The highlighted p values indicate statistically significant results.

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

	pCO_2 ≤45 mm Hg (n = 130)	pCO_2 >45 mm Hg (n = 33)	p value
ΔpCO_2, mm Hg	−1.0 (4.3)	−8.8 (12.5)	**0.015**
ΔFEV1, L	0.10 (0.3)	0.05 (0.2)	0.670
ΔRV, L	−0.49 (1.7)	−0.40 (1.4)	0.701
ΔDLCO, mm Hg	0.2 (0.7)	0.52 (0.5)	0.238
Δ6-MWT, m	37.4 (105.4)	40.0 (153.0)	0.882
ΔmMRC (points)	−0.3 (1.03)	−0.2 (1.0)	0.537
ΔCAT (points)	−2.2 (6.3)	−2.0 (6.0)	0.729
ΔSGRQ (points)	−2.4 (9.2)	−2.6 (10.2)	0.628

Data are represented as mean (SD). FEV1, forced expiratory volume in 1 s; RV, residual volume; DLCO, diffusion capacity of the lung for carbon monoxide; pCO_2, partial pressure of carbon dioxide; 6-MWT, 6-min walking test; mMRC, modified Medical Research Council; CAT, COPD assessment test; SGRQ, St. George's Respiratory Questionnaire. The highlighted p value indicates statistically significant results.

fingertip sampling accurately reflect arterial blood gases with no significant differences between the two different techniques, thus suggesting that capillary blood gas analysis provides excellent accuracy and precision. Based on this analysis, in our study protocol, data on capillary CO_2 were requested. However, there was no information available on whether the gas analysis was performed by earlobe or fingertip sampling or if arterial gas analysis was performed [22]. The Zephyr® valve system (Pulmonx) and the Spiration Valve System (Olympus) were used for 81.2% and 18.8% of patients, respectively.

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 one-way valves. We used the following MCIDs: improvement of FEV1 of at least 10%, reduction of RV equal or more 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 7 points as previously described [23–27].

Statistical Analysis

Categorical variables are presented as absolute numbers and percentages. Continuous variables are presented as means and standard deviations because they are normally distributed. Comparisons of baseline characteristics and occurrence of adverse events between both groups were performed using the independent t test or χ^2 test. The Wilcoxon rank test was performed to evaluate changes in lung function parameters, exercise capacity, and quality of life of each group at the 3-month follow-up. The mean difference (Δ) was determined as the difference between the

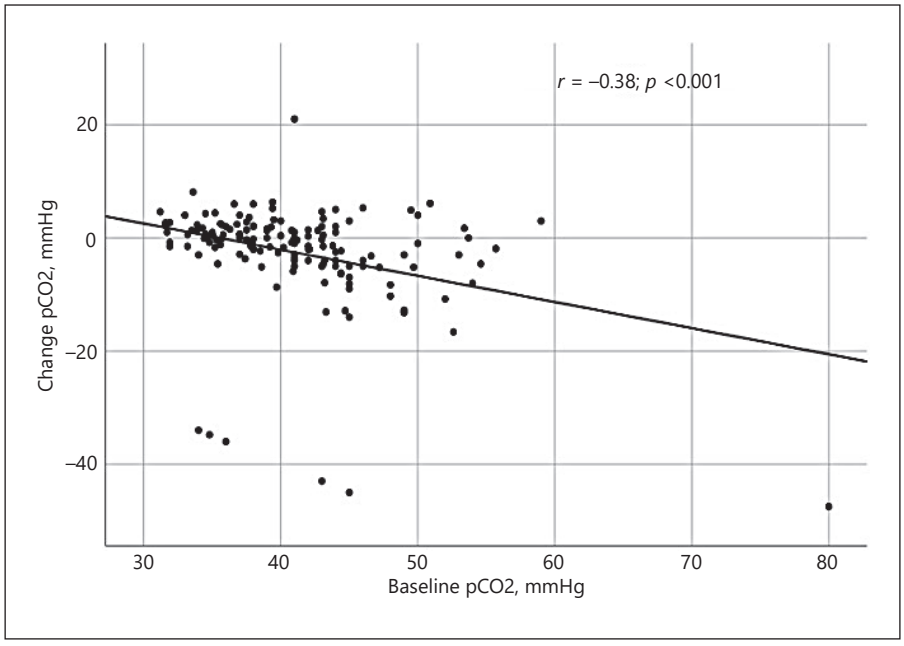

Fig. 1. Correlations between baseline pCO_2 and change in pCO_2 at the 3-month follow-up. pCO_2, partial pressure of carbon dioxide.

baseline and the 3-month follow-up value. Comparisons of lung function, exercise capacity, and quality of life data between the ΔpCO_2 groups were performed using the independent *t* test. Pearson's correlation analysis was performed to detect correlations between changes in pCO_2 and changes in FEV1, RV, and DLCO. *p* values of <0.05 were considered significant. All statistical analyses were performed using SPSS software (version 24.0.0.0; IBM, Armonk, NY, USA).

Results

Demographic Data at Baseline

Between September 2017 and October 2020, a total of 197 patients underwent ELVR with valves (Table 1). Among these patients, 157 had pCO_2 ≤45 mm Hg at baseline, and 40 patients had pCO_2 >45 mm Hg. The mean age and sex ratios were similar between the two groups. There were significant differences between the groups in the frequency of cardiovascular diseases (pCO_2 ≤45 mm Hg: 17.8% vs. pCO_2 >45 mm Hg: 35.0%; $p = 0.018$) and diabetes mellitus type II (pCO_2 ≤45 mm Hg: 3.2% vs. pCO_2 >45 mm Hg: 12.5%; $p = 0.017$). At baseline, patients with pCO_2 >45 mm Hg presented with significantly lower FEV1 (29.6 ± 10.4%) and higher RV (271.9 ± 60.1%) values than did those with pCO_2 ≤45 mm Hg (FEV1: 31.6 ± 9.5%, $p = 0.001$; RV: 249.8 ± 52.5%, $p = 0.001$). At the 3-month follow-up, 27 patients (17.0%) in the pCO_2 ≤45 mm Hg group and 7 (17.5%) in the pCO_2 >45 mm Hg group dropped out.

Outcome at 3 Months after ELVR with One-Way Valves

Table 2 demonstrates the clinical outcomes in relation to pCO_2 after valve implantation at the 3-month follow-up. After one-way valve treatment, only patients with pCO_2 >45 mm Hg showed a significant decrease of pCO_2 from baseline (52.2 ± 6.2 mm Hg) to the 3-month follow-up (43.7 ± 8.6 mm Hg; $p = 0.008$), whereas patients with pCO_2 ≤45 mm Hg presented with similar levels of pCO_2 between timepoints. Compared with that at baseline, RV improved significantly at the 3-month follow-up in both groups ($p < 0.001$), while FEV1 improved significantly at the 3-month follow-up only in patients with pCO_2 ≤45 mm Hg ($p < 0.001$ to baseline). Similarly, 6-MWT values improved significantly at the 3-month follow-up only in patients with pCO_2 ≤45 mm Hg (from 274.8 ± 104.4 m to 326.6 ± 102.9 m; $p = 0.037$). The mMRC, CAT, and SGRQ scores significantly decreased only in patients with pCO_2 ≤45 mm Hg (mMRC: 2.9 ± 0.9 to 2.5 ± 0.9, $p = 0.004$; CAT: 24.8 ± 6.7 to 22.5 ± 7.0; $p = 0.004$; SGRQ: 57.4 ± 15.9 to 55.0 ± 16.4, $p = 0.028$).

As shown in Table 3, compared to patients with pCO_2 ≤45 mm Hg, those with hypercapnia showed a significant decrease of 8.8 mm Hg in pCO_2 at the 3-month follow-up ($p = 0.015$), thus returning to normal levels by the 3-month follow-up. No further significant differences were observed between the groups in terms of lung function parameters, exercise capacity, or quality of life. To further investigate the decrease in the pCO_2, a separate correlation analysis was

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

	pCO_2 ≤45 mm Hg, *n*/*N* (%)	pCO_2 >45 mm Hg, *n*/*N* (%)	*p* value
FEV1 (L), MCID ≥+10%	22/130 (16.9)	6/33 (18.2)	0.675
RV (L), MCID ≥0.43 L	50/130 (38.4)	17/33 (51.5)	0.578
6-MWD (m), MCID ≥+26 m	50/130 (38.5)	17/33 (51.5)	0.580
SGRQ (points), MCID ≤−7 points	33/130 (25.4)	10/33 (30.3)	0.445

MCID, minimal clinically important difference; pCO_2, partial pressure of carbon dioxide; FEV1, forced expiratory volume in 1 s; RV, residual volume; 6-MWD, 6-min walking distance; SGRQ, St. George's Respiratory Questionnaire.

Table 5. Adverse events during the 3-month follow-up period after endobronchial implantation of valves

Adverse events	pCO_2 ≤45 mm Hg (*n* = 130)	pCO_2 >45 mm Hg (*n* = 33)	*p* value
ICU, *n* (%)	6 (4.6)	1 (3.0)	0.972
Mechanical ventilation, *n* (%)	4 (3.1)	0 (0.0)	0.415
Death, *n* (%)	1 (0.8)	0 (0.0)	0.687
Sepsis, *n* (%)	2 (1.5)	0 (0.0)	0.568
Bleeding, *n* (%)	1 (0.8)	0 (0.0)	0.687
Pneumonia, *n* (%)	6 (4.6)	2 (6.1)	0.346
AECOPD, *n* (%)	18 (13.8)	2 (6.1)	0.588
Pneumothorax, *n* (%)	27 (20.8)	4 (12.1)	0.862

Data are represented as *n* (%). pCO_2, partial pressure of carbon dioxide; ICU, intensive care unit; AECOPD, acute exacerbation of chronic obstructive pulmonary disease.

performed. Patients who were more hypercapnic at baseline showed a greater reduction in pCO_2 after ELVR with valves ($r = -0.38$, $p < 0.001$), as displayed in Figure 1. In addition, the reduction in pCO_2 was significantly correlated with changes in FEV1 ($r = -0.23$, $p = 0.007$). No significant correlations were observed between changes in pCO_2 and changes in RV, DLCO, 6-MWT, mMRC, CAT, or SGRQ results after treatment (data not shown).

Table 4 depicts the responders with MCIDs in outcome measures between pCO_2 groups. There were no significant differences in outcomes between patients with pCO_2 ≤45 mm Hg and those with pCO_2 >45 mm Hg.

Adverse Events

There were no significant differences between the groups at the 3-month follow-up (Table 5). In detail, the most frequent complication in both groups was pneumothorax (pCO_2 ≤45 mm Hg, 20.8% vs. pCO_2 >45 mm Hg, 12.1%; $p = 0.862$). An acute exacerbation of COPD occurred in 13.8% of patients with pCO_2 ≤45 mm Hg and in 6.1% of patients with pCO_2 >45 mm Hg ($p = 0.588$). Pneumonia and admission to an intensive care unit were low in both groups. No deaths were observed among the hypercapnic patients. One patient (0.8%) with pCO_2 ≤45 mm Hg died after 3 months due to cardiac infarction.

Discussion/Conclusion

Clinical evidence on tracking the efficacy and safety of ELVR with valves in patients with hypercapnia is scarce, and there is no consensus whether those patients should be offered the treatment at all. To our knowledge, this is the first systematic analysis of emerging data from a national prospective clinical study, which thoroughly describes the treatment outcomes after ELVR among patients with hypercapnia. Our main result was that patients with pre-existing hypercapnia (pCO_2 >45 mm Hg) experienced a significant decrease in the pCO_2 levels after ELVR with valves at the 3-month follow-up. Higher degrees of hypercapnia were significantly correlated with a higher reduction in the pCO_2 after treatment. Furthermore, we observed a significant decline in RV among patients with pCO_2 >45 mm Hg.

In recent randomized trials of ELVR with valves, rigorous evidence suggested that valve implantation improved lung function, exercise capacity, and quality of life in patients with emphysema [9, 28]. In the EMPROVE study [9], there was a mean decrease in RV of 402 mL and a mean increase in FEV1 of 101 mL, while in the LIBERATE study [28], there was a mean reduction in RV of 490 mL and a mean increase in FEV1 of 104 mL. In our study, we found a comparable mean reduction in RV of 490 mL in the normocapnic group and 400 mL in the hypercapnic group, as well as a mean increase in FEV1 of 100 mL in the normocapnic group and 50 mL in the hypercapnic one [9, 28]. Patients with hypercapnic respiratory failure had a non-significant improvement of 40 m in the 6-MWT, similar to the normocapnic group, whereas it increased at the 6-month follow-up in the LIBERATE study by 13 m [28] and decreased in the EMPROVE study by 4 m [9]. Interestingly, we observed similar improvements in both groups concerning the quality of life as measured using mMRC, CAT, and SGRQ. In contrast, in both LIBERATE [28] and EMPROVE [9] studies, patients treated with valves experienced greater improvements of at least 7.5 points in SGRQ, which were higher than those obtained in our study. However, it is important to highlight that both of these studies strictly excluded patients with pCO_2 >45 mm Hg, which could explain these slight differences. Since our patients were not examined under the highly controlled conditions of randomized studies, it is interesting to note that our findings in a real-world setting had improvements similar to those of randomized controlled studies. Interestingly, responder rates with MCIDs revealed no significant differences in the outcome between groups. However, the MCID of FEV1 was lower than that reported in other randomized trials [29] since a significant fraction of patients showed improvements close below the cut-off levels. Therefore, these patients were not counted as responders.

Recent recommendations on the prerequisites for valve implantation suggest that, at first glance, patients with hypercapnia should be excluded from this type of therapy because they are presumably at a higher risk of unsolicited complications [30]. Nevertheless, Slebos et al. [30] suggest a re-evaluation of these patients after 3 months of non-invasive mechanical ventilation for considering valve therapy. However, the exact effects of valve implantation in hypercapnic patients are still limited. In line with our findings, in a retrospective analysis, Trudzinski et al. [13] found a significant decrease in pCO_2 from 55 mm Hg to 50 mm Hg after 3 months in 13 hypercapnic patients treated with one-way valves. There are also some case reports supporting the view that ELVR with valves might be a treatment strategy for patients with severe bullous emphysema and concomitant severe hypercapnia [31, 32].

Hypercapnia is associated with severe emphysematous destruction and hyperinflation of COPD lungs, mainly due to a loss of elastic recoil and collapse of small airways [33]. Theoretically, ELVR effectively improves hyperinflation and respiratory mechanics so that CO_2 can be exhaled more effectively by an improved airflow distribution [34]. In agreement, in a recent review on surgical lung volume reduction and hypercapnia, the authors mentioned six papers that stated that this approach can lead to significant amelioration of hypercapnia [35]. O'Brien et al. [5] observed a significantly greater reduction in the pCO_2 levels after LVRS in hypercapnic patients than in normocapnic patients. In addition, Wisser et al. [6] alluded that LVRS was a promising approach in hypercapnic patients since pCO_2 was found to be 41.2 mm Hg at 1 month after surgery and remained stable during a long-term follow-up. In a more recent study on the efficacy of LVRS in patients with chronic hypercapnia, Shade et al. [36] described that patients who were more hypercapnic preoperatively showed greater reductions in pCO_2 after surgery. The investigators reported relationships between the postoperative decrease in pCO_2 and airflow, global inspiratory muscle strength, and diffusion capacity. Interestingly, we also found that severe hypercapnia was correlated with a higher reduction in pCO_2 levels after treatment. Furthermore, we showed that the reduction in pCO_2 was significantly correlated with increases in FEV1. Considering the underlying mechanisms, valve therapy aims to block the inspiratory airflow into the targeted, hyperinflated region of the lung while allowing air to escape during exhalation. The reduction of hyperinflated areas of the lung produces space for the remaining lung to expand, thus resulting in improved lung mechanics and respiratory volume. Therefore, one might argue that valve therapy does yield an advantage also for hypercapnic patients by producing benefits similar to LVRS.

In our study, hypercapnic patients did not have significant improvements in FEV1, 6-MWT, or quality of life, while these criteria improved significantly in the normocapnic group. We strongly believe that the low number of patients in the hypercapnic group might have had a substantial impact on the effect of the presumable improvements. On the other hand, there are many underlying mechanisms that contribute to the development of hypercapnia in COPD patients. Mathews et al. [37] sug-

gested that hypercapnia can be caused by multiple factors, but reduced ventilatory capacity, low muscle reserve, and chronic hyperventilation seem to be critical factors for the occurrence of hypercapnia. It is well known that chronic hypercapnic respiratory failure exposes patients to an increased risk of adverse events [7]. Findings of the NETT revealed higher mortality rates in patients with hypercapnia after LVRS [7]. In a prospective study of 275 patients with COPD, Yang et al. [38] showed that hypercapnic respiratory failure was associated with a poor prognosis and a lower survival rate. In particular, they described that patients with hypercapnia had a median survival period of 5 years, which was shorter than the survival period of 6.5 years for normocapnic patients [38]. In studies on LVRS in hypercapnic patients, Wisser et al. [6] reported a 30-day mortality rate of 9.1%, and O'Brien et al. [5] observed only a single death in 31 patients. Interestingly, in our study, no single deaths were observed in hypercapnic patients, although patients were followed up for only 3 months. We found no significant differences in complications between the two groups; however, the data should be interpreted with caution as the number of hypercapnic patients included was small and unbalanced in comparison to the normocapnic patient group. The most common adverse event in both groups was the occurrence of pneumothorax, which was in line with the results of randomized trials involving normocapnic patients [39].

The main strength of our analysis is that we systematically examined the safety and efficacy of one-way valves in patients with chronic hypercapnic respiratory failure. However, there are certain limitations. As current guidelines recommend, hypercapnic patients, who are subsequently treated with non-invasive pressure ventilation, might be reconsidered for valve therapy [21]. However, due to our design, our study did not collect data on rates of long-term non-invasive positive pressure ventilation, a well-established treatment option for hypercapnia in COPD [40, 41], and certainly an important initial consideration when evaluating such patients for a possible lung volume reduction. Patients who are subsequently treated with non-invasive pressure ventilation should be reconsidered for valve therapy [21]. 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. 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. In the database, there was no information available whether blood gas analysis was derived from arterial or capillary blood. As a matter of fact, it is known that different techniques accurately show blood gas analysis with good accuracy and precision, and so more information on sampling techniques may not have an impact on the results [22]. The resulting non-consecutive inclusion may have served as a potential bias. Furthermore, we observed a dropout rate of 17.2% in the normocapnic group and 17.5% in the hypercapnic group, which might have reduced the statistical power of our results. However, since patients with pCO_2 >45 mm Hg had only a marginal role in previous studies on ELVR with valves, we believe that our findings can add relevant information for the treatment of hypercapnic patients.

Based on these findings, ELVR with valve treatment is an efficacious treatment strategy for patients with chronic hypercapnic respiratory failure. No deaths occurred during the 3-month follow-up period; however, it is important to mention that there were few patients with hypercapnia. In addition to improvements in lung function parameters, the pCO_2 level decreased significantly after ELVR with valve treatment at the 3-month follow-up. Randomised trials are warranted to substantiate the significance of our novel findings.

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Statement of Ethics

This study protocol was reviewed and approved by the Review Board of the Charité Universitätsmedizin Berlin, approval number (EA2_149_17) and registered with the German Clinical Trials Registry (DRKS00021207). The presented work was conducted according to Declaration of Helsinki. Each patient consented to participate in the study.

Conflict of Interest Statement

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. S. Eisenmann reports non-financial support from Pulmonx, outside the submitted work. R.-H. Hübner reports personal fees and non-financial support from Olympus and Pulmonx, outside the submitted work. The other authors have no conflicts of interest to declare.

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Author Contributions

Analysis and interpretation of data and study supervision: Ralf-Harto Hübner and Pavlina Lenga. Critically revising the article: Pavlina Lenga, Christian Grah, Christoph Ruwwe-Glösenkamp, Jacopo Saccomanno, Jens Rückert, Stephan Eggeling, Sven Gläser, Sylke Kurz, Stephan Eisenmann, Marcus Krüger, Bernd Schmidt, Paul Schneider, Stefan Andreas, Marc Hinterthaner, Joachim Pfannschmidt, Andreas Gebhardt, Franz Stanzel, Angélique Holland, Andreas Kirschbaum, Birgit Becke, and Ralf-Harto Hübner. Statistical analysis: Hübner Ralf and Pavlina Lenga.

Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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