Utility of Rehabilitation prior to bronchoscopic lung volume reduction – post-hoc analysis of the VENT trial

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ORIGINAL ARTICLE

TITLE: Utility of Rehabilitation prior to bronchoscopic lung volume reduction – post-hoc analysis of the VENT trial

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**Take home message:** Pulmonary rehabilitation is an essential tool for patients with severe COPD. Given the only modest improvements in exercise capacity, mandatory requirements for rehabilitation before bronchoscopic lung volume reduction should be reconsidered.

**ABSTRACT:**

**Background and objective:** Rehabilitation programs are a valuable treatment modality for patients with chronic-obstructive pulmonary disease (COPD) to increase exercise capacity and quality of life. The utility of pulmonary rehabilitation (PR) prior to bronchoscopic lung volume reduction (BLVR) is unclear.

**Methods:** We performed a post-hoc analysis of the VENT trial, the first multicenter randomized trial comparing the safety and efficacy of BLVR. Patients completed a PR program prior to BLVR over 6-10 weeks and maintained by daily practice, consisting of endurance training, strength training and upper/lower limb exercise. Lung function and exercise parameters (six-minute-walking testing; 6-MWT) were assessed before and after rehabilitation and we tried to identify predictors for PR benefit.

**Results:** Lung function and exercise capacity of 403 patients (mean age 63.3 ± 7.4 years, 37.5% female, mean FEV₁ 30.1 ± 7.6 l) were analyzed. Exercise capacity significantly improved from 331.6 ± 98.8 to 345.6 ± 95.3m (p<0.001) in 6-MWT with 40.3% showing clinically meaningful improvements. Patients also experienced less dyspnea after 6-MWT, while pulmonary function parameters did not change significantly overall. Patients with lower exercise capacity at screening (6-MWT <250m) benefited more from PR. The indication and prerequisites for BLVR were still present in all patients after PR.

**Conclusion:** The national mandatory requirements for rehabilitation prior to BLVR, which apply to all COPD patients, should be reconsidered and specified for COPD patients who really benefit.

**Short title:** rehabilitation prior to bronchoscopic lung volume reduction

**Keywords:** bronchoscopic lung volume reduction, endoscopic lung volume reduction, endobronchial valves, COPD, pulmonary rehabilitation, rehabilitation

**Word count:** 3050 (20.111), abstract: 227 words

**Conference presentation:** These data have been presented previously in abstract form. (“The value of pre-trial rehabilitation before endoscopic lung volume reduction – Analysis of the VENT trial.” Konstantina Kontogianni, Ralf Eberhardt, Daniela Gompelmann, Maren Schuhmann, Arschang Valipour, Felix J.F. Herth. European Respiratory Journal 2014 44: P3046).
INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) remains a major healthcare issue with a global impact, currently being the fourth leading cause of death worldwide. [1] The high impact of morbidity and mortality associated with COPD includes a significant economic burden, with COPD accounting for more than 50% of the direct costs of respiratory disease, and an impact on productivity at work and home. At an individual level, the rapid downward spiral of symptom-induced inactivity, muscle deconditioning and subsequent weakness associated with the disease affects quality of life, with reduced social interaction, depression and in many cases death. [2] In its more severe manifestation, emphysema, pathological damage to the lung parenchyma and destruction of elastin leads to air trapping and hyperinflation of the lungs and is the main mechanism of exertional dyspnea. [3, 4]

Medical management of COPD involves multiple strategies, starting with smoking cessation, pulmonary rehabilitation (PR) and self-management, vaccination, pharmacological therapy to improve airflow, reduce symptoms, exacerbations and minimize infections. Oxygen supplementation is required for hypoxemic patients and long-term non-invasive ventilation is offered to patients with hypercapnia and respiratory failure. [1] Pulmonary rehabilitation programs improve exercise tolerance, complementing pharmacotherapy, to reverse systemic musculoskeletal dysfunction in severe COPD patients. [5] For patients with advanced emphysema refractory to medical management, the next steps are non-invasive and invasive surgical options in appropriately selected patients. Hyperinflation is addressed by several techniques of lung volume reduction. [6–9]

Patients being considered for interventions such as bronchoscopic lung volume reduction (BLVR) or surgical lung volume reduction (LVRS) must be clinically stable to safely undergo the procedure. Clinical trials evaluating BLVR required PR prior to randomization to maximize function prior to intervention. [6, 7] Currently, health insurance companies worldwide require mandatory PR prior to BLVR not only with the idea that this may improve the general condition before BLVR as a safety measure, but also to prevent patients from needing interventional therapy after conservative treatment options have been exhausted. Despite this requirement, to our knowledge, there is no data available that proves the benefit of PR before BLVR. [10] This requirement can affect both the timing of the procedure and the willingness to receive this guideline-recommended non-invasive therapy. [1] Furthermore, this creates disparity issues in countries or regions where PR is not easily accessed. Finally, in a setting where pulmonary function may improve following BLVR, enabling more vigorous cardiac and peripheral muscle training, it is unclear whether it is justified to make PR a mandatory prerequisite in the pre-procedural setting.

We evaluated the impact of pulmonary rehabilitation prior to BLVR through a post-hoc analysis of data from the Valve for Emphysema Palliation Trial (VENT) [7, 11], the first multicenter, randomized clinical trial comparing the safety and efficacy of endoscopic lung volume reduction with Zephyr valves in heterogeneous emphysema versus medical treatment. All enrolled patients underwent a detailed rehabilitation program before being randomized to either the treatment or control group.
METHODS

A total of 492 patients with severe emphysema were randomized in the study with a US cohort of 321 patients [7] and a European cohort of 171 patients [11].

The inclusion and exclusion criteria have been previously published [12] and are summarized here for the ease of the reader: age 40 - 75 years, diagnosis of heterogeneous emphysema, forced expiratory volume in one second (FEV$_1$) 15 - 45% predicted, total lung capacity (TLC) > 100% predicted, residual volume (RV) > 150% predicted, body-mass index (BMI) ≤ 31.1 kg/m$^2$ (men) or ≤ 32.3 kg/m$^2$ (women), partial pressure of carbon dioxide (PaCO$_2$) < 50 mmHg and partial pressure of oxygen (PaO$_2$) > 45 mmHg on ambient air, and post-rehabilitation 6-minute walking distance (6-MWD) ≥ 140 meters. Patients with diffusion capacity (DLCO) < 20% predicted, presence of giant bullae or alpha-antitrypsin deficiency, previous thoracotomy, excessive sputum, severe pulmonary hypertension, active infection, or unstable cardiac conditions were excluded.

Study Design

Patients signed an Institutional Review Board (IRB) or Ethics Committee (EC) approved informed consent form before undergoing the screening evaluations. Prior to randomization, patients who had not completed PR within the previous 60 days underwent 6-8 weeks of pulmonary rehabilitation and optimized medical management at the discretion of the treating physician within the context of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [1]. Patients who had recently (within the last 60 days) completed PR and provided documentation of the rehabilitation program were eligible for baseline testing.

The rehabilitation program offered 2 visits at the rehabilitation center per week with a minimum attendance requirement of 75% and included lower and upper limb endurance training as well as a lower and upper limb strength training with the following components:

- Lower limb endurance training (on a treadmill, on an exercise bicycle, or both, depending on the treating therapist’s assessment of individual circumstances).
- Upper limb endurance training (exercises using some form and level of resistance for each hand (e.g. dumbbells or Thera-Bands).
- Lower and upper limb strength training (exercises involving some form and level of resistance (e.g. dumbbells or Thera-Bands).

Following completion of the in-clinic PR program, the patients were encouraged to follow a home maintenance program at least twice a week. The program consisted of the following components:

- Lower Limb Endurance Training (walking for 20-30 minutes substituted for treadmill or exercise bicycle).
- Upper Limb Endurance Training (as recommended by PR therapist, intended to be similar to in-clinic program).
- Lower and Upper Limb Strength Training (as recommended by PR therapist, intended to be similar to in-clinic program).

Patients who successfully completed their PR program underwent baseline assessments and, if they continued to meet all protocol entry criteria, were randomized 2:1 to either the treatment or control group. Evaluations performed at screening and repeated after PR
were: supplemental O₂ use, vital signs, electrocardiogram, spirometry, body plethysmography, DLCO, PaO₂, PaCO₂, O₂ saturation, and 6-MWT.

Subjects randomized to the treatment group underwent Zephyr Valve placement procedure; these data have been previously published [7, 11] and are not the subject of this manuscript. The data presented here are for the impact of pulmonary rehabilitation on aspects of lung function measures and exercise capacity.

**Statistical analysis**

All analyses have been performed using IBM SPSS version 28 (IBM Corporation, Somers, New York). Data are presented as mean ± standard deviation (SD) or median (min-max and interquartile range [IQR]). Frequency data are presented as n and percentage. Comparison of clinical data between pre- and post-rehabilitation was performed by two-sided student’s t-test for paired data.

Data of 6-MWT were only compared pre- and post-rehabilitation when complete data sets were available (Borg dyspnea pre and post score, fatigue pre and post score, 6-MWD). In addition, subgroup analyses were performed for patients with a 6-MWD increase after PR ≥ the minimal clinically important difference (MCID) of 26m [13] vs. <26m and a screening 6-MWD < 250m vs. ≥ 250m. A multiple linear regression analysis was performed to identify predictors for 6-MWD increase after PR according to clinical relevance for the following parameters: age, BMI, sex, FEV₁, RV, FVC, TLC, RV/TLC, DLCO, PaCO₂, PaO₂, all parameters of 6-MWT (Borg scores, 6-MWD).

Due to the explorative nature of the study, p-values were interpreted descriptively. No adjustment for multiple testing was performed. p-values <0.05 were considered statistically significant.

**RESULTS**

**Patient selection and characteristics**

Of 492 subjects enrolled in the VENT study (171 European cohort, 321 US cohort), we excluded subjects who did not complete pulmonary rehabilitation (n=35) or did not perform a screening evaluation.

Finally, 403 patients were included in the analysis (table 1). The mean 6-MWD before PR in the group with complete data sets for 6-MWT (n=350) was 331.6 ± 98.8m (median 326.0 m, min 100 m, max 715m).

**Outcome after pulmonary rehabilitation**

After completion of PR, all patients underwent reassessment of lung function and exercise capacity (table 2). Lung function parameters like FEV₁ (no change) and RV (+0.01l) did not significantly change after rehabilitation overall. The 6-minute-walking distance increased significantly by 14.0 m (p<0.001), but less than the MCID of 26 meters [13], and patients suffered from less dyspnea after 6-MWT: Borg dyspnea post 6-MWT decreased from 4.5 ±
2.1 to 4.3 ± 2.2 points (p=0.018). A total of 40.3% (141/350) achieved the MCID for 6-MWT. PaCO₂ worsened minimally (+ 0.4mmHg, p=0.038) after rehabilitation.

**Predictors for success of pulmonary rehabilitation**

The group of patients that reached MCID for 6-MWT after PR, also showed a statistically significant increase of FVC (64.8 ± 14.8 to 67.0 ± 15.2 %, p=0.009), but not of other lung function parameters. The dyspnea pre score decreased from 1.4 ± 1.5 to 1.1 ± 1.4 points (p=0.046). When comparing the patient group with 6-MWD increase ≥26m vs. <26m, no statistically significant differences in screening parameters (lung function, blood gas) were detected, but patients with 6-MWD increase ≥26m had lower 6-MWD at screening (298.4 ± 95.4 vs. 354.0 ± 94.9 m, p<0.001).

Patients with a screening 6-MWD < 250m (n=74) improved significantly from 203.5 ± 38.4 to 244.2 ± 60.7 m (p<0.001) in 6-MWT and showed also an increase of FVC (59.3 ± 13.4% to 61.8 ± 14.5%, p=0.042) without improvement of other lung function parameters. In contrast to this, patients with a screening 6-MWD ≥250m (n=276) did not improve significantly in terms of exercise capacity (366.0 ± 80.0 to 372.8 ± 83.9 m, p=0.065). As expected, patients with screening 6-MWD <250m were older, had worse lung function (lower FEV₁, lower FVC, higher RV) and blood gas compared to patients with screening 6-MWD ≥250m.

The regression analysis revealed the 6-MWD prior to PR (p<0.001, b=-0.543) (**figure 1**) and DLCO (p=0.025, b=0.132) (**figure 2**) as predictors for therapy success in terms of exercise capacity improvement.

**DISCUSSION**

To our knowledge, this is the first study to evaluate the effects of pulmonary rehabilitation in patients that are candidates for bronchoscopic lung volume reduction. We have shown in a large cohort of 403 patients with severe COPD and emphysema that pulmonary rehabilitation has no effect on pulmonary function in accordance with existing data, while it improves exercise capacity, particularly in patients with lower 6-MWD at screening. After PR, all patients still had the indication and prerequisites for BLVR.

The rehabilitation program offered to the VENT study cohort included the typical guideline based aspects of PR programs [14], including endurance training as well as strength training with upper and lower limb exercises. The American Thoracic Society and European Respiratory Society [14] recommend PR programs to last a minimum of 8 weeks to achieve effects on exercise performance and quality of life, while studies report different time spans of PR programs of 4-52 weeks [15]. Based on the observed significant improvement for 6-MWT, we assume that the PR program offered to the VENT cohort was efficient, especially as the program was based on the National Emphysema Treatment Trial (NETT) program with the same content and duration. Our patient cohort is an exemplary cohort for BLVR but may have more severe lung function impairment and hyperinflation than usual COPD patient cohorts studied in PR trials and therefore have less benefit.
The reported benefits of PR include reduced hospital admissions, reduced dyspnea and improved exercise capacity, limb muscle strength and quality of life [14]. Patients with hyperinflation also benefit from PR with clinically meaningful improvements in 6-MWD and St. George’s Respiratory Questionnaire (SGRQ) [16, 17]. A large review by the Cochrane Collaboration [15] looking at 65 studies and 3822 participants to assess effects of PR on COPD patients showed that PR programs provide clinically meaningful improvements for quality of life, SGRQ (mean difference [MD] total – 6.9 points) and exercise capacity (MD +43.9m). Only a few studies evaluated effects of PR on lung function and the changes reported were small (FEV₁ increase from 57.3% to 60.8% after 3 years [16], FEV₁ decline of 18 ± 22ml per year over 7 years [17], FEV₁ increase from 47.3 ± 9.4 to 55.6 ± 9.0 % after 12 weeks [18]). Consistent with these effects, pulmonary function parameters did not improve overall after PR in the presented trial, while exercise capacity increased. The overall improvement in exercise capacity of 14 meters was less in our patients than the reported MCID for 6-MWD of 25-54 meters [13, 19]; 40.3% achieved the MCID for 6-MWD of 26m [13].

Improvements in exercise capacity were accompanied by a minimal increase of PaCO₂ which was not clinically significant. Patients may have exhausted their ventilatory reserve by overexerting themselves.

The regression analysis and subgroup analyses showed that patients with reduced exercise capacity at screening were responders for PR in terms of improved 6-MWD. One can imagine that patients with more limited exercise capacity and quality of life may have a higher motivation and potential to improve their training state. Supervised training and professional guidance have greater effects in patients who are severely limited by dyspnea at rest, as this was the parameter that improved in the 6-MWT, and PR programs may help these patients more than patients that have already good skills in breathing manoeuvres and exercise training.

In addition, diffusion capacity was shown as significant, but very weak predictor for PR benefit. In emphysema patients, diffusion capacity correlates with emphysema extent, so it seems logical that better diffusion capacity directly and indirectly may allow for better exercise performance. It should be noted that this regression analysis was only carried out with a few parameters and, for example, parameters such as depression or quality of life were not included at all, although they could certainly explain a part of the rehabilitation outcome.

Our findings are in contrast to other studies that tried to identify prognostic features for PR success and drop-out in COPD patients. The baseline state was evaluated as a poor predictor for PR response, although dyspnea symptom scores were positively and younger age, current smoking and lower health status negatively associated with PR outcome [20, 21].

Although prediction of PR success needs further evaluation, the findings are encouraging for physically impaired COPD patients and may indicate, that it could be useful to perform PR before BLVR in patients with more impaired but still preserved exercise capacity. However, one must bear in mind that this does not fully reflect the real-world-setting, where patients with a 6-MWD <140m (excluded from the VENT trial!) are also often treated
with BLVR and are severely impaired in their ability to walk. Further studies are needed to evaluate which patients benefit most from PR and if there is a 6-MWD-threshold that has to be taken into account.

Despite the requirement of pulmonary rehabilitation prior to BLVR, to our knowledge, there is no data available that proves the benefit of PR before BLVR. However, data are available for patients undergoing surgical lung volume reduction (LVRS). Debigré et al. showed that patients undergoing PR before LVRS achieved significant improvements in 6-MWD, quality of life, peak work rate, peak oxygen consumption, endurance time and muscle strength in a home-based exercise training, although there was no improvement in lung function [22]. Similar findings were reported in the NETT Trial that included 1218 emphysema patients who underwent pulmonary rehabilitation before LVRS with significant improvements for 6-MWD (76 feet = 23 meters), quality of life (SGRQ -3.5 points) and dyspnea. [23] Apart from a slight decrease in hyperinflation (RV/TLC decrease of 0.6%), no improvement in lung function was observed (FEV1 -0.1 ± 3.7 %, RV/TLC -0.6 ±5.1 %). Patients who had previously undergone PR, had smaller improvements. Approximately 10% of patients improved by PR that were no longer willing to undergo LVRS (which does not mean, that they were not eligible any more). The authors of NETT concluded, that pulmonary rehabilitation is important in the preparation and selection of patients for LVRS, as exercise levels improved significantly [23].

While we agree with the assumption that some patients will reach a general condition through PR in which they are better equipped and fit enough for BLVR, it is worth noting that benefits of PR diminish after 6-12 months if there are no maintenance strategies [19] and patients will likely revert to their pre-PR status, however, BLVR will have been delayed. On the other hand, the improvement in lung function after BLVR improves the dominant ventilatory limitation to exertion present in COPD and likely results in more effective cardiac and peripheral muscle training. The greater ability and willingness to participate in PR following BLVR plausibly results in greater improvements in exercise capacity and quality of life, with longer-lasting effects.

Finally, the inability of some patients to participate effectively in pulmonary rehabilitation due to disabling symptoms or frailty which may be improved with BLVR, or due to limited access to PR facilities in certain countries or geographic regions, would eliminate this potential treatment option, and increase treatment disparities, in the setting of mandatory PR requirement.

The effect of the timing of PR, if better pre- or post-BLVR, should be assessed in future studies. It is also important to identify the group of COPD patients who will benefit most from PR, so that individualised recommendations can be made. Until then, it should be up to the treating physician to recommend pulmonary rehabilitation before or after BLVR, depending on the individual patient’s general condition and circumstances.

The main limitation of this study is that assessing the benefit of pulmonary rehabilitation was not the primary objective and endpoint of this study. Data for 6-MWT and other parameters were incomplete and may have influenced the results. On the other hand, this
was a prospective study with parameters collected under strict study conditions, so the results appear reliable.

What this study cannot answer is the question if PR has an influence on the outcome of BLVR. This needs to be addressed in future studies.

**CONCLUSION**

Supervised pulmonary rehabilitation prior to BLVR in patients with emphysematous type of COPD resulted, overall, in modest improvements in exercise capacity and dyspnea. These findings challenge the recommendation that all patients being considered for BLVR should undergo pulmonary rehabilitation. Patients with low but preserved exercise capacity may benefit most from PR prior to BLVR and the general condition in these patients may be improved as a safety measure. The idea of preventing patients from needing interventional therapy after PR should be discarded, as none of the patients improved to the point where bronchoscopic lung volume reduction was no longer possible or necessary. Finally, our data suggest that PR prior to BLVR procedures may not be a critical prerequisite in all patients.
Author Contributions
Judith Brock: Literature research, data analysis, statistics, interpretation of results, Writing – original draft
Felix Herth: Conceptualization, Supervision, Resources, Writing – review & editing
Konstantina Kontogianni, Frank Sciurba, Gerard Criner: Conceptualization, supervision, interpretation of results, Writing – review & editing

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Conflicts of Interest Statement:
Judith Brock has received honoraria and consultation fees from Boehringer Ingelheim, Astra Zeneca, streamed up!, Intuitive Surgical Inc, Berlin Chemie, Olympus. There is no conflict of interest regarding this manuscript.
Konstantina Kontogianni has received honoraria for teaching courses from Olympus, for lectures from Berlin-Chemie and Boston Scientific, for attending meetings from Astra Zeneca. She has no conflicts of interest regarding this manuscript.
Frank Sciurba reports institutional grant supports from Sanofi/Regeneron, Astra Zeneca, Verona Pharma, Nuvaira, Gala Therapeutics and personal payments for advisory boards of Sanofi/Regeneron, Astra Zeneca, Verona Pharma, Galxo Smith Kline, Boehringer Ingelheim.
Gerard Criner reports grants from Pulmonx and honorarium for teaching activities. All activities are outside the submitted work.
Felix Herth reports consulting fees from Pulmonx outside the submitted work.
All authors confirm no conflicts of interest regarding this manuscript.

Data Availability Statement
The data will be made available on reasonable request from the corresponding author.

Ethics Approval Declaration:
The Study protocol was reviewed and approved by the Institutional Ethics Committee and Institutional Review Boards at all participating study sites. All patients gave written informed consent for the scientific use of their medical records. The study was conducted in accordance to the Declaration of Helsinki.
Abbreviations:

6-MWD 6-minute-walking distance
6-MWT 6-minute-walking testing
BMI body mass index
BLVR bronchoscopic lung volume reduction
COPD Chronic Obstructive Pulmonary Disease
DLCO diffusion capacity of carbon monoxide
FEV₁ forced expiratory volume in 1 second
FVC forced vital capacity
GOLD Global Initiative for Chronic Obstructive Lung Disease
IQR interquartile range
LVRS Lung volume reduction surgery
MCID minimal clinically important difference
MD mean difference
NETT National Emphysema Treatment Trial
PaO₂ partial pressure of oxygen
PaCO₂ partial pressure of carbon dioxide
PR Pulmonary rehabilitation
RV residual volume
SD standard deviation
SGRQ St. George’s Respiratory Questionnaire
TLC total lung capacity
US United States
VENT valve for emphysema palliation trial
**TABLES**

**Table 1. Baseline Characteristics**

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>N</th>
<th>mean ± SD or “n” and percentage</th>
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<tbody>
<tr>
<td>Age (years)</td>
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<td>63.3 ± 7.4</td>
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<td>Sex (female) (n, %)</td>
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<td>154 38.2</td>
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<tr>
<td>BMI (kg/m²)</td>
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<td>24.4 ± 3.9</td>
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<tr>
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<td>Treatment (vs. control)</td>
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<tr>
<td><strong>Target lobe</strong></td>
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<td>Right upper lobe (n, %)</td>
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<td>207 51.4</td>
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<td>Right lower lobe (n, %)</td>
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<td>53 13.2</td>
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<td><strong>Blood gas</strong></td>
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<td>PaO₂</td>
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<td>PaCO₂</td>
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<td><strong>Lung function</strong></td>
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<td>FEV₁ (l)</td>
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<tr>
<td>FEV₁ (%)</td>
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<td>RV (l)</td>
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<td>RV (%)</td>
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<td>DLCO (%)</td>
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<td><strong>Symptoms and exercise capacity</strong></td>
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<td>6-MWD</td>
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<td>6-MWT Dyspnea pre^</td>
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<td>6-MWT Dyspnea post^</td>
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<td>4.6 ± 2.2</td>
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<tr>
<td>6-MWT Fatigue pre^</td>
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<tr>
<td>6-MWT Fatigue post^</td>
<td>370</td>
<td>3.1 ± 2.3</td>
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*Data are presented as mean ± SD or “n” and percentage.

Abbreviations: BMI, body mass index; PaO₂, partial pressure of oxygen; PaCO₂, partial pressure of carbon dioxide; FEV₁, forced expiratory volume in 1 second; RV, residual volume; FVC, forced vital capacity; TLC, total lung capacity; DLCO, diffusion capacity of carbon monoxide; 6-MWD, 6-minute-walk distance; 6-MWT, 6-minute-walk testing.

^ Dyspnea and fatigue were measured pre and post exertion using the modified BORG 0-10 scale.
Table 2. Lung Function Measures Before and After Pulmonary Rehabilitation

<table>
<thead>
<tr>
<th>Outcome parameter</th>
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<th>After Rehabilitation (mean ± SD)</th>
<th>p-value</th>
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<td>0.89 ± 0.27</td>
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<td>FEV₁ (%)</td>
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<td>FVC (%)</td>
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<tr>
<td>RV (l)</td>
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<td>4.86 ± 1.19</td>
<td>4.87 ± 1.15</td>
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<tr>
<td>RV (%)</td>
<td>393</td>
<td>225.18 ± 52.29</td>
<td>226.33 ± 49.31</td>
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<tr>
<td>RV/TLC (%)</td>
<td>394</td>
<td>63.5 ± 8.7</td>
<td>63.4 ± 8.4</td>
<td>0.744</td>
</tr>
<tr>
<td>TLC (l)</td>
<td>394</td>
<td>7.64 ± 1.48</td>
<td>7.68 ± 1.45</td>
<td>0.194</td>
</tr>
<tr>
<td>TLC (%)</td>
<td>385</td>
<td>126.34 ± 16.20</td>
<td>126.72 ± 16.87</td>
<td>0.597</td>
</tr>
<tr>
<td>6-MWD</td>
<td>350</td>
<td>331.6 ± 98.8</td>
<td>345.6 ± 95.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6-MWT Dyspnea pre^</td>
<td>350</td>
<td>1.2 ± 1.3</td>
<td>1.2 ± 1.3</td>
<td>0.585</td>
</tr>
<tr>
<td>6-MWT Dyspnea post^</td>
<td>350</td>
<td>4.5 ± 2.1</td>
<td>4.3 ± 2.2</td>
<td>0.018</td>
</tr>
<tr>
<td>6-MWT Fatigue pre^</td>
<td>350</td>
<td>1.1 ± 1.5</td>
<td>1.1 ± 1.5</td>
<td>0.378</td>
</tr>
<tr>
<td>6-MWT Fatigue post^</td>
<td>350</td>
<td>3.2 ± 2.3</td>
<td>3.1 ± 2.3</td>
<td>0.455</td>
</tr>
<tr>
<td>PaO₂</td>
<td>395</td>
<td>67.0 ± 13.1</td>
<td>67.6 ± 13.2</td>
<td>0.164</td>
</tr>
<tr>
<td>PaCO₂</td>
<td>398</td>
<td>39.0 ± 6.8</td>
<td>39.4 ± 7.0</td>
<td>0.038</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD.
Abbreviations: FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity; 6-MWD, 6-minute-walk distance; 6-MWT, 6-minute-walk testing; PaO₂, partial pressure of oxygen; PaCO₂, partial pressure of carbon dioxide.

^ Dyspnea and fatigue were measured pre and post exertion using the modified BORG 0-10 scale.
References


Figure 1. Scatter plot of 6-MWT distance at screening in m (x-axis) and change in walking distance after pulmonary rehabilitation in m (y-axis)
Figure 2. Scatter plot of diffusion capacity (DLCO) at screening in % (x-axis) and change in walking distance after pulmonary rehabilitation in m (y-axis)