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Impact and timing of pulmonary rehabilitation in patients undergoing bronchoscopic lung volume reduction with endobronchial valves: A multicentre randomized controlled trial in patients with severe emphysema

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Abstract

Background and Objective: Both bronchoscopic lung volume reduction with endobronchial valves (BLVR-EBV) and pulmonary rehabilitation (PR) are effective treatments for improving exercise capacity and patient-reported outcomes in patients with severe Chronic Obstructive Pulmonary Disease (COPD). According to current recommendations, all BLVR-EBV patients should have undergone PR first. Our aim was to study the effects of PR both before and after BLVR-EBV compared to BLVR-EBV alone.

Methods: We included patients with severe COPD who were eligible for BLVR-EBV and PR. Participants were randomized into three groups: PR before BLVR-EBV, PR after BLVR-EBV or BLVR-EBV without PR. The primary outcome was change in constant work rate cycle test (CWRT) endurance time at 6-month follow-up of the PR groups compared to BLVR-EBV alone. Secondary endpoints included changes in 6-minute walking test, daily step count, dyspnoea and health-related quality of life.

Results: Ninety-seven participants were included. At 6-month follow-up, there was no difference in change in CWRT endurance time between the PR before BLVR-EBV

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and BLVR-EBV alone groups (median: 421 [IQR: 44; 1304] vs. 787 [123; 1024] seconds, $p = 0.82$) or in any of the secondary endpoints, but the PR after BLVR-EBV group exhibited a smaller improvement in CWRT endurance time (median: 107 [IQR: 2; 573], $p = 0.04$) and health-related quality of life compared to BLVR-EBV alone.
Conclusion: The addition of PR to BLVR-EBV did not result in increased exercise capacity, daily step count or improved patient-reported outcomes compared to BLVR-EBV alone, neither when PR was administered before BLVR-EBV nor when PR was administered after BLVR-EBV.

KEYWORDS
Bronchoscopic lung volume reduction, chronic obstructive pulmonary disease, COPD, endobronchial valves, pulmonary rehabilitation

INTRODUCTION

Exercise intolerance is one of the main disabling symptoms in patients with chronic obstructive pulmonary disease (COPD). In this patient group, impaired exercise capacity is due to ventilatory restraints, but also physical inactivity and lower-limb muscle dysfunction are important contributing factors.[1] Several treatment options are available to address these components in patients with COPD, including bronchoscopic lung volume reduction with endobronchial valves (BLVR-EBV) and pulmonary rehabilitation.[2]

BLVR-EBV has been established as an advanced treatment option in patients with severe COPD to reduce pulmonary hyperinflation and thereby alleviate ventilatory restraints.[3] Pulmonary rehabilitation addresses factors such as deconditioning and is an effective treatment option to improve dyspnoea and enhance exercise capacity, daily physical activity level and quality of life.[4] Moreover, pulmonary rehabilitation is a cornerstone in the preoperative optimization of patients before lung volume reduction surgery or lung transplantation in order to aim for a reduction of peri- and post-operative risks.[5,6]

According to expert panel recommendations, also all patients who are eligible for BLVR-EBV are required to have undergone pulmonary rehabilitation and/or be enrolled in a structured physical therapy plan.[7] However, compared to lung volume reduction surgery, BLVR-EBV is a less-invasive approach for reducing pulmonary hyperinflation. And while pulmonary rehabilitation can significantly improve exercise capacity and quality of life in patients with severe pulmonary hyperinflation, it could be hypothesized that pulmonary rehabilitation may be more effective in this patient group after pulmonary hyperinflation has been reduced as a result of increased ventilatory reserve capacity and potential higher training loads.[8,9]

To date, no studies have investigated the impact of a combined pulmonary rehabilitation and BLVR-EBV program, nor have studies determined the timing of pulmonary rehabilitation in relation to the intervention. Therefore, our objective was to investigate the effects of pulmonary rehabilitation both before and after BLVR-EBV on exercise capacity and patient-reported outcomes compared to BLVR-EBV alone.

SUMMARY AT A GLANCE

Our findings suggest that a combination of pulmonary rehabilitation and bronchoscopic lung volume reduction with endobronchial valves (BLVR-EBV) may not provide additional benefits compared to BLVR-EBV alone at a group-level. Future challenges lie in selecting patients for whom a combined rehabilitation trajectory would be beneficial.

METHODS

Study design

Subjects were enrolled in this randomized controlled trial (NCT03474471) between July 2018 and June 2022 at two sites (University Medical Center Groningen, the Netherlands, and Ciro, Horn, the Netherlands). Participants were randomized in a 1:1:1 fashion immediately after baseline visit to one of the following groups: pulmonary rehabilitation before BLVR-EBV (group 1), pulmonary rehabilitation after BLVR-EBV (group 2) or BLVR-EBV without pulmonary rehabilitation (group 3). BLVR-EBV was scheduled directly following completion of the pulmonary rehabilitation program, but pulmonary rehabilitation was scheduled approximately 2 months after BLVR-EBV due to the elevated risk of a pneumothorax for the first 6–8 weeks following treatment. The study was approved by the ethics committees at both sites (METc 2018/241) and written informed consent was obtained from all subjects.

Study population

All participants were ex-smokers with severe emphysema, who did not follow a pulmonary rehabilitation program

in the last 12 months before study entry and who were considered eligible for BLVR-EBV. Key inclusion criteria included forced expiratory volume in 1 s (FEV_1) equal to or less than 45%, residual volume (RV) greater than 175% predicted, emphysematous destruction of the target lobe greater than 50% at −910 Hounsfield Unit and a fissure integrity of the target lobe greater than 95% as measured by quantitative computed tomography analysis. A complete overview of the inclusion and exclusion criteria is provided in the online supplement (Appendix S1 in the Supporting Information).

Randomization and blinding

This was an unblinded study, and randomization was conducted in permuted blocks of three without stratification. Computer-generated randomization lists were developed by a University Medical Center Groningen employee who was not involved in the study and who subsequently created sealed envelopes. The site investigators enrolled patients and obtained randomization codes by opening the sealed envelopes, based on the inclusion site and study patient number. The block size of three was concealed from the investigators throughout the study.

Bronchoscopic lung volume reduction with endobronchial valves

In BLVR-EBV, one-way valves (Zephyr, PulmonX, CA, USA) were placed in all segmental bronchi of a hyperinflated lung lobe. The endobronchial valve allows air to leave on exhalation, but not to enter on inspiration, which results in deflation of the treated lung lobe and reduction of hyperinflation as a consequence.[7]

All procedures were performed at either the University Medical Center Groningen, the Netherlands or the Maastricht University Medical Center, the Netherlands, in accordance with the most recent recommendations.[7]

Pulmonary rehabilitation

Pulmonary rehabilitation is an interdisciplinary patient-tailored program to reduce symptoms, and improve both the physical and psychological condition of patients with chronic respiratory diseases.[10] These personalized treatment programs included at least structured physical exercise training (incorporating both resistance and endurance training), functional training, dyspnoea and exacerbation management, educational sessions, relaxation techniques, time and energy management strategies, sputum mobilization techniques, psychosocial counselling and nutritional counselling. Rehabilitation programs could be followed either in a clinical or outpatient setting.

All pulmonary rehabilitation programs were performed in line with the current ATS/ERS guidelines and had a mean duration of 8–10 weeks.[10] Participants followed a pulmonary rehabilitation program in one of the dedicated pulmonary rehabilitation centres in the Netherlands: Beatrixoord (Haren), Radboud University Medical Center (Nijmegen), Merem Medical Rehabilitation (Hilversum), Revant (Breda) or Ciro (Horn). The program at each pulmonary rehabilitation center was evaluated for completeness, and participants who failed to complete the full pulmonary rehabilitation program were excluded.

Primary outcome

The primary outcome was change in constant work rate cycle test (CWRT) endurance time of the pulmonary rehabilitation groups compared to BLVR-EBV alone at 6 month follow-up. CWRT was executed at a workload of 75% of the peak work capacity as determined by an incremental cycle test.[11] Patients were instructed to maintain a pedalling cadence of 60 rpm and cycle as long as possible. The test was terminated when the pedalling rate could no longer be sustained. During the follow-up visits, the test was also terminated when the endurance time exceeded 60 min or 500% of the baseline endurance time.

Sample size calculation

The minimal important difference in CWRT endurance time is 105 seconds,[12] and we estimated the standard deviation at 130 s. This resulted in a sample size of 26 patients per group to detect a 105-s difference in CWRT endurance time between the groups with 80% power at a two-sided significance level of 0.05. Anticipating a dropout rate of 20%, we aimed to enrol 32 patients per group.

Secondary outcomes

Pulmonary functions tests included spirometry, body plethysmography and the 6-minute walking test (6-MWT), which were all performed in line with the current recommendations.[13–15] The modified Medical Research Council dyspnoea scale (mMRC) was used to rate dyspnoea severity,[16] and the St. George's Respiratory Questionnaire (SGRQ) was used to assess quality of life.[17] The 30 s chair-to-stand test was performed as a measure of lower body strength.[18] Daily physical activity was measured with an accelerometer (DynaPort MoveMonitor, McRoberts BV, The Hague, the Netherlands) that was worn for seven consecutive days. Responders were defined as participants who met the minimal important difference of the outcome measure, which are 105 s for the CWRT endurance time, 26 m for the 6-MWT and a reduction of

TABLE 1 Baseline characteristics.

	Group 1, PR before BLVR-EBV ($n = 34$)	Group 2, PR after BLVR-EBV ($n = 33$)	Group 3, BLVR-EBV ($n = 30$)	p
Demographic characteristics				
Sex, male (%)	26.5	51.5	33.3	0.09
Age, years	62.9 ± 6.0	63.5 ± 8.4	62.4 ± 5.6	0.83
Pack years	39.9 ± 23.6	41.1 ± 20.1	41.1 ± 17.3	0.96
Pulmonary characteristics				
FEV_1, L	0.73 ± 0.24	0.77 ± 0.22	0.76 ± 0.20	0.71
FEV_1, % predicted	27.1 ± 8.2	26.4 ± 6.5	27.1 ± 7.4	0.89
FVC, L	2.53 ± 0.80	2.78 ± 0.84	2.66 ± 0.60	0.42
FVC, % predicted	72.9 ± 18.8	72.3 ± 13.2	72.9 ± 13.8	0.98
RV, L	4.87 ± 0.85	5.18 ± 1.12	4.87 ± 1.16	0.38
RV, % predicted	253.1 ± 44.5	251.3 ± 49.0	242.1 ± 39.6	0.58
RV/TLC, ratio	0.64 ± 0.06	0.64 ± 0.07	0.63 ± 0.06	0.77
DL_{CO}, % predicted	34.4 ± 8.9	37.7 ± 9.5	37.1 ± 7.8	0.30
PaO_2, kPa	9.15 ± 1.25	9.41 ± 1.35	9.40 ± 1.08	0.62
$PaCO_2$, kPa	5.38 ± 0.54	5.42 ± 0.71	5.41 ± 0.68	0.97
Exercise capacity and physical activity				
Peak work capacity, W	33.0 ± 16.0	39.4 ± 19.1	41.4 ± 18.2	0.14
Peak VO_2, mL/kg/min	11.3 ± 2.1	10.9 ± 2.5	11.1 ± 2.2	0.82
Cycle endurance time, s	293.1 ± 224.8	261.2 ± 159.4	269.2 ± 129.0	0.75
6-MWT, m	308.3 ± 86.8	319.1 ± 88.7	320.9 ± 82.0	0.82
Chair-to-stand test, *n*	11.2 ± 3.4	10.7 ± 2.8	11.0 ± 2.7	0.73
Steps per day, *n*	2370 ± 1187	2664 ± 1674	2687 ± 1662	0.74
Patient-reported outcomes				
mMRC score	2.97 ± 0.58	2.70 ± 0.59	2.70 ± 0.70	0.14
SGRQ total score	59.0 ± 13.5	58.0 ± 12.9	62.4 ± 10.0	0.35

Note: Data are displayed as mean ± SD or percentage. One-way ANOVA and X^2 tests were performed to test for statistically significant differences between the groups.
Abbreviations: 6-MWT, 6-minute walking test; BLVR-EBV, bronchoscopic lung volume reduction with endobronchial valves; DLCO, diffusing capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; mMRC, modified Medical Research Council Dyspnoea; $PaCO_2$, arterial carbon dioxide tension; PaO_2, arterial oxygen tension; PR, pulmonary rehabilitation; RV, residual volume; SGRQ, St. George's Respiratory Questionnaire; TLC, total lung capacity; VO_2, oxygen uptake.

8 points for the SGRQ in patients with severe COPD.[12,19,20] Before randomization, participants were also asked about their preferred study group: pulmonary rehabilitation before BLVR-EBV, pulmonary rehabilitation after BLVR-EBV, BLVR-EBV without pulmonary rehabilitation, or no preference.

Statistical analysis

We used an intention-to-treat approach for our primary and secondary endpoints, utilizing the available data. All data analyses were performed with the use of SPSS (version 28, IBM, NY, USA), and a p-value of <0.05 was considered statistically significant. To assess differences among the baseline data of the three study groups, one-way ANOVA and chi-square tests were employed. We performed linear and logistic regression models adjusted for sex and baseline value to evaluate the differences between the groups regarding changes from baseline to follow-up. The regression analysis assumptions were checked and considered valid if the residuals were normally distributed. Chi-square tests were used to examine the disparities between the groups concerning adverse events.

RESULTS

Study population

A total of 97 participants were included and randomized into the different study groups. Thirty-four participants were assigned to pulmonary rehabilitation before BLVR-EBV (group 1), 33 to pulmonary rehabilitation after BLVR-EBV (group 2) and 30 to BLVR-EBV alone (group 3). The baseline characteristics of each group's participants are presented in Table 1 and Table S1 in the Supporting Information. Three participants of group 2 declined pulmonary rehabilitation after BLVR-EBV and had therefore missing visit 2 data. A study flowchart is depicted in Figure 1. Except for daily step count in

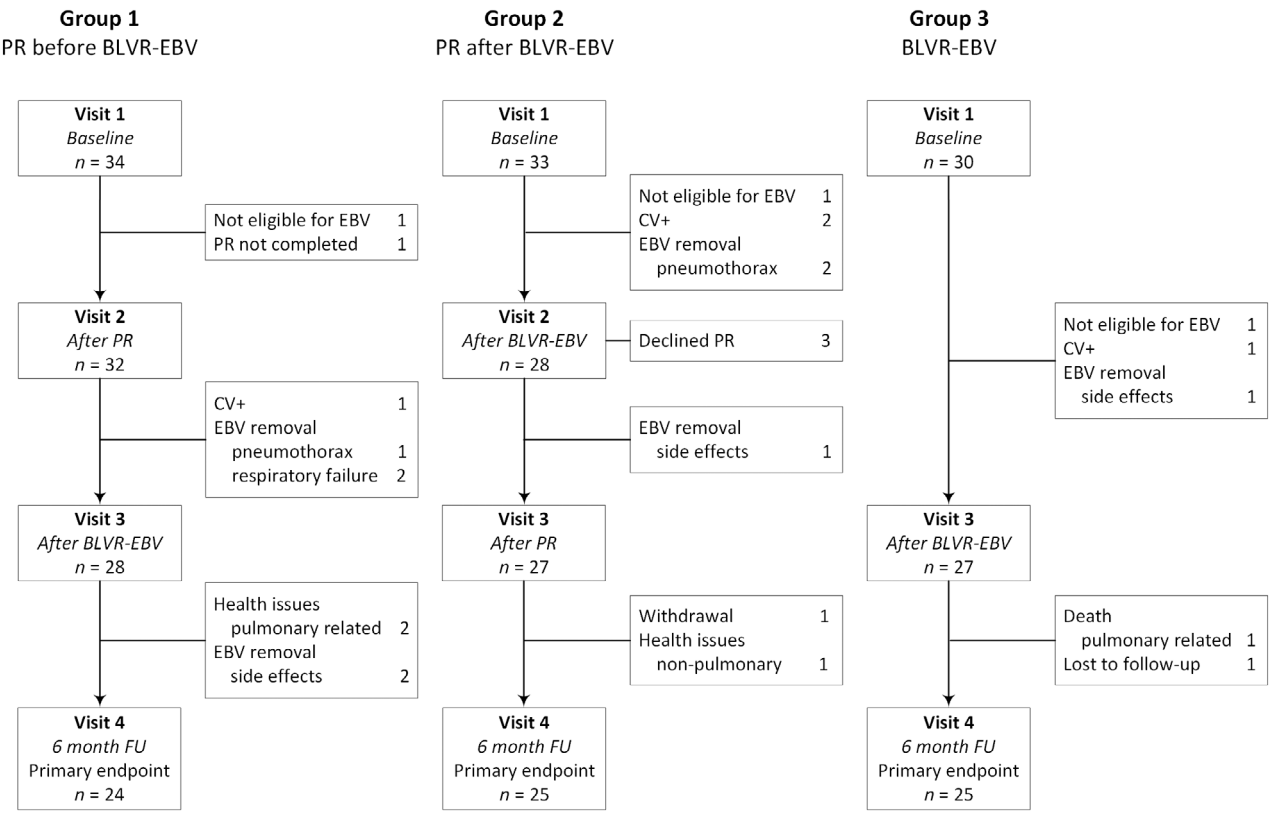

FIGURE 1 Study flowchart. BLVR-EBV, bronchoscopic lung volume reduction with endobronchial valves; CV, collateral ventilation; EBV, endobronchial valves; PR, pulmonary rehabilitation.

TABLE 2 Change in outcomes at 6 months follow-up compared to baseline for the pulmonary rehabilitation groups compared to the non-rehabilitation group.

	Group 1, PR before BLVR-EBV ($n = 24$)	p	Group 2, PR after BLVR-EBV ($n = 25$)	p	Group 3, BLVR-EBV ($n = 25$)
Pulmonary function tests					
Δ FEV_1, L	0.15 ± 0.17	0.70	0.10 ± 0.13	0.11	0.17 ± 0.18
Δ FVC, L	0.41 ± 0.59	0.62	0.38 ± 0.40	0.25	0.50 ± 0.47
Δ RV, L	−0.76 ± 0.61	0.77	−0.65 ± 0.71	0.67	−0.70 ± 0.72
Exercise capacity and physical activity					
Δ Cycle endurance time, s	421 (44; 1304)	0.82	107 (2; 573)	0.04*	787 (123; 1024)
Responders CWRT, %	66.7	0.96	52.0	0.07	80.0
Maximal CWRT, %	41.7	0.64	28.0	0.21	44.0
Δ 6-MWT, m	55.6 ± 81.8	0.93	34.2 ± 58.5	0.20	54.0 ± 60.2
Responders 6-MWT, %	62.5	0.89	53.8	0.33	68.0
Δ Chair-to-stand test, *n*	2.0 (0.0; 4.0)	0.80	2.0 (0.3; 4.8)	0.90	2.0 (0.0; 4.5)
Δ Steps per day, *n*	270 (−113; 835)	0.54	171 (−515; 426)	0.05	583 (83; 1352)
Patient-reported outcomes					
Δ mMRC score	−0.63 ± 0.58	0.60	−0.44 ± 0.71	0.38	−0.56 ± 0.65
Δ SGRQ total score	−14.8 ± 15.2	0.43	−9.9 ± 14.6	0.05*	−18.8 ± 12.3
Responders SGRQ, %	66.7	1.00	57.7	0.23	76.0

Note: Data are displayed as mean ± SD, median (IQR) or percentage. Linear and logistic regression models adjusted for sex and baseline value were performed to test for statistically significant differences between the rehabilitation groups and the non-rehabilitation group.

Abbreviations: 6-MWT, 6-minute walking test; BLVR-EBV, bronchoscopic lung volume reduction with endobronchial valves; CWRT, constant work rate cycle test; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; maximal CWRT, cycle endurance time of five times the baseline time; mMRC, modified Medical Research Council Dyspnoea; PR, pulmonary rehabilitation; RV, residual volume; SGRQ, St. George's Respiratory Questionnaire; Δ, change compared to baseline.

groups 1 and 2, all outcomes measures at the 6-month follow-up showed statistically significant changes compared to baseline in all three study groups.

Pulmonary rehabilitation before and after BLVR-EBV compared to BLVR-EBV alone

At the 6-month follow-up, we found no significant differences in the change in cycle endurance time between the BLVR-EBV alone group and the group that underwent PR before BLVR-EBV. The group that underwent PR after BLVR-EBV exhibited a smaller improvement in cycle endurance time compared to the BLVR-EBV alone group, along with a less pronounced reduction in SGRQ score (Table 2). Furthermore, there were no significant differences between the rehabilitation groups and the BLVR-EBV alone group in terms of the increase in the 6-MWT, chair-to-stand test, daily step count or mMRC score.

Notably, we also observed no differences between the groups in change in cycle endurance time, daily step count or patient-reported outcomes immediately after treatment(s) (Figure 2 and Table S2 in the Supporting Information).

Patient preferences

Before randomization, participants were asked about their preferred timing for pulmonary rehabilitation in relation to BLVR-EBV. The majority of participants (60.4%) favoured rehabilitation after BLVR-EBV, whereas 14.6% chose no rehabilitation. Of the remaining participants, 12.5% preferred rehabilitation before BLVR-EBV and 12.5% had no preference regarding timing.

After the final visit, participants allocated to group 3 (BLVR-EBV alone) were offered the opportunity to follow a rehabilitation program afterwards. However, none of the participants opted to utilize this option.

Adverse events

One study participant died in group 3 (BLVR-EBV alone) as a result of a contralateral pneumothorax 4 months after treatment. In group 1 (pulmonary rehabilitation before BLVR-EBV), one participant had two serious COPD exacerbations. In both rehabilitation groups, one participant

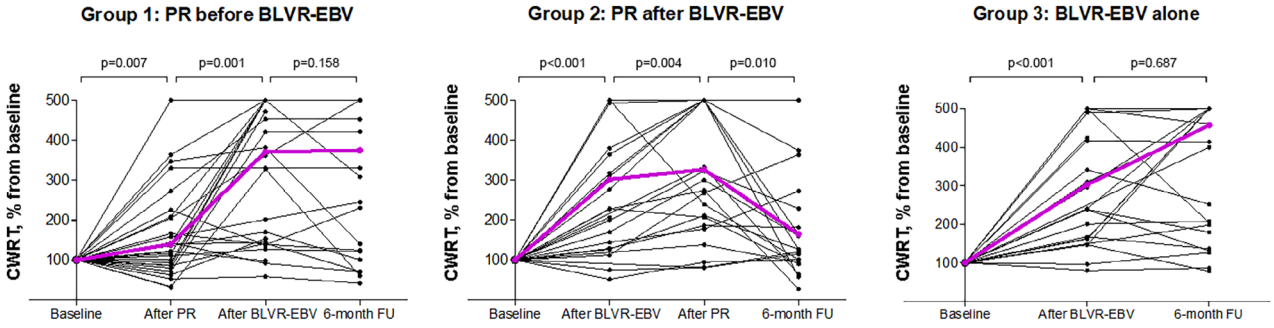

FIGURE 2 Individual data on relative cycle endurance time at the different time points for all study groups. CWRT, constant work rate cycle test, the median is shown in purple.

TABLE 3 Adverse events in all study groups.

	Group 1, PR before BLVR-EBV ($n = 34$)	Group 2, PR after BLVR-EBV ($n = 30$)	Group 3, BLVR-EBV ($n = 33$)	p
Death	-	-	1 (3.0)	0.38
Severe exacerbation				0.50
• 1× severe exacerbation, *n* (%)	6 (17.6)	5 (16.7)	4 (12.1)	
• 2× severe exacerbations, *n* (%)	1 (2.9)	-	-	
Pneumothorax				0.63
• 1× pneumothorax, *n* (%)	6 (17.6)	4 (13.3)	2 (6.1)	
• 2× pneumothorax, *n* (%)	1 (2.9)	-	-	
Rebronchoscopy				0.44
• 1× valve replacement, *n* (%)	6 (17.6)	6 (20.0)	5 (15.2)	
• 2× valve replacement, *n* (%)	-	1 (3.3)	-	
• Valve removal, *n* (%)	3 (8.8)	2 (6.7)	1 (3.0)	

Note: X^2 tests were performed to test for statistically significant differences between the groups.
Abbreviations: BLVR-EBV, bronchoscopic lung volume reduction with endobronchial valves; PR, pulmonary rehabilitation; severe exacerbation, pneumonia or COPD exacerbation requiring hospitalization.

underwent two revision bronchoscopies for valve replacement. We found no significant differences between the groups in the number of patients that experienced a severe exacerbation, pneumothorax or required a rebronchoscopy. All data on the occurrence of adverse events in the different study groups are shown in Table 3.

DISCUSSION

This is the first randomized controlled trial to explore the impact of combining pulmonary rehabilitation with BLVR-EBV compared to BLVR-EBV as a standalone intervention. Our study showed that the addition of pulmonary rehabilitation to BLVR-EBV did not result in increased exercise capacity, improved patients-reported outcomes or an increase in daily step count compared to BLVR-EBV alone, neither when pulmonary rehabilitation was administrated before BLVR-EBV nor when PR was administered after BLVR-EBV.

We also did not find differences in cycling endurance time immediately after the treatments (visit 3), when the effect of pulmonary rehabilitation is presumably most pronounced.[21] Interestingly, a further increase in exercise capacity and quality of life was seen in those performing pulmonary rehabilitation after BLVR-EBV, as well as in those who underwent BLVR-EBV after pulmonary rehabilitation (Figure 2, Table S2 in the Supporting Information). However, the improvements after both treatments compared to baseline were similar to the outcomes of the group that underwent BLVR-EBV without pulmonary rehabilitation.

In addition to improving physical capacity, pulmonary rehabilitation also focuses on coping skills and adjustments in daily life to enable patients to enhance their functional capacity.[10] However, also no differences were found between the non-rehabilitation and rehabilitation groups in dyspnoea severity (mMRC) and quality of life (SGRQ), both immediately after the treatments and at 6-month follow-up.

There are various factors that may have contributed to these findings. One hypothesis is that the severe lung function impairment is the primary cause of impaired exercise capacity in this particular subgroup of patients with COPD. Therefore, the impact of pulmonary rehabilitation may be relatively small in comparison to the substantial improvement in lung function that results from BLVR-EBV. We observed similar findings in a previously published substudy of this trial, in which we obtained cardiac magnetic resonance imaging before and after BLVR-EBV. Even though there was a significant increase in cardiac output owing to enhanced cardiac preload and contractility, we could not find any association between cardiac improvement and exercise capacity.[22] This could be due to the fact that lung function is still the limiting factor during exercise in this particular population, leading to improvements in cardiac function to be overshadowed.

Additionally, patients' expectations or outcomes from BLVR-EBV may also have an impact on their motivation for rehabilitation, since our study shows relatively limited results for pulmonary rehabilitation alone when compared to prior research (Table S3 in the Supporting Information).[9] It is possible that patients may be less motivated for rehabilitation if they have high expectations for the forthcoming BLVR-EBV, or if they are already experiencing substantial improvement from BLVR-EBV. This is reflected in our study, as three participants in group 2 declined rehabilitation after BLVR-EBV, and the lack of interest in rehabilitation among participants in group 3 after their final visit, while none of the participants in group 1 declined BLVR-EBV after rehabilitation. This contrasts with the NETT trial's results, where some participants showed such significant improvement that they chose to decline lung volume reduction surgery after completing their rehabilitation program.[8] Of note is that our study employed a different study design whereby participants were already committed to BLVR-EBV, thereby making these outcomes not entirely comparable.

Another possible explanation could be that participants who underwent pulmonary rehabilitation had a longer follow-up period compared to those who only received BLVR-EBV and were therefore more at risk for developing granulation tissue. The development of granulation tissue is a common adverse event in BLVR-EBV that may worsen over time, and granulation tissue is the most common finding in patients who experience loss of initial treatment effect.[23] However, no differences were seen in improvements of pulmonary function tests between both groups at 6 months, nor in the number of revision bronchoscopies for valve replacement.[24]

A priori, it was hypothesized that the improved lung function resulting from BLVR-EBV would shift the limiting factor of exercise capacity towards deconditioning, which is specifically addressed during pulmonary rehabilitation. Therefore, it is somewhat unexpected that participants who completed pulmonary rehabilitation after BLVR-EBV did not exhibit greater absolute and relative improvements in CWRT endurance time compared to those who underwent pulmonary rehabilitation before BLVR-EBV.

To our knowledge, no studies have been performed that evaluate the timing of pulmonary rehabilitation in patients with COPD who are scheduled for treatments, such as lung transplantation and surgical or bronchoscopic lung volume reduction. One RCT studied the effects of pulmonary rehabilitation after lung transplantation compared to standard of care, but no studies have been performed thus far that compare outcomes of pulmonary rehabilitation pre- and post-treatment.[24]

In our study, a clear majority of participants expressed a preference for rehabilitation after BLVR-EBV. While it is possible that those who preferred to undergo pulmonary rehabilitation after BLVR-EBV were more likely to participate in the study, this factor should be taken into account, particularly as BLVR-EBV is a less-invasive treatment compared to lung volume reduction surgery or lung transplantation, and our study did not reveal any clear risks or benefits associated with not undergoing rehabilitation beforehand.

Despite clear improvements in lung function and exercise capacity, daily physical activity did not increase in both pulmonary rehabilitation groups at 6-month follow-up. Similar results have been reported after 4 weeks of aclidinium/formoterol treatment in patients with COPD, and after pulmonary rehabilitation.[25,26] A continued physical activity coaching program might to be needed to establish an increase in physical activity.[27]

It might also be interesting to explore the possibility of a split rehabilitation program, with part of the rehabilitation program taking place before and part after BLVR-EBV, but this aspect has not been investigated yet.

Our study has limitations (see Table S4 in the Supporting Information). The main limitation is that a substantial portion of participants achieved the maximum duration time for the CWRT, which presents a challenge in analysing the primary outcome. However, we observed similar results in the other outcome measures where no maximum values were applicable, such as 6-MWT and SGRQ.

Another major limitation is that the dropout rate (23.7%) was higher than we had anticipated (20%), consequently, we included respectively 24, 25 and 25 patients per group instead of the calculated 26 and therefore the study might be slightly underpowered. This may have limited our ability to detect significant differences between the groups. It would therefore be valuable to validate our findings in a larger cohort. The dropout was mostly due to the inability to complete BLVR-EBV, such as the presence of collateral ventilation or a persistent pneumothorax which necessitated valve removal, and in some patients valve removal was necessary due to the adverse effects they encountered. Although the study was partially conducted during the COVID-19 pandemic, which resulted in a longer duration of the study than initially intended, it did not affect the timelines between both treatments or the treatments themselves, nor did it result in the drop-out of patients.

Our study featured a uniform approach of the most comprehensive pulmonary rehabilitation program in the Netherlands for all participants. These programs are tailored to patients with complex chronic pulmonary diseases and multiple treatable traits, but not all participants had a treatment indication for this specific multidisciplinary program. It is conceivable that our results would have been different if we exclusively included participants with an indication for the most comprehensive program. Furthermore, our study incorporated patients who had undergone rehabilitation in the past and were motivated to participate again. It has been demonstrated that subsequent rehabilitation is less impactful than the initial treatment, which may have played a role in our findings.[8]

Finally, it should be noted that these conclusions are based on group-level analysis and may not necessarily apply to individual cases. In line with clinical practice, we observed substantial individual variances in response to the treatments in our study (Figure 2). Therefore, it would be our recommendation to consider the additional value and optimal timing of pulmonary rehabilitation on an individual level.

In conclusion, the combination of pulmonary rehabilitation with BLVR-EBV did not result in increased exercise capacity, improved patient-reported outcomes or increased daily step count compared to BLVR-EBV alone. Future challenges lie in selecting patients for whom a combined rehabilitation trajectory would be beneficial and developing methods to sustain the effects of a rehabilitation program for an extended period of time in this patient population.

AUTHOR CONTRIBUTIONS

Marieke C. van der Molen: Data curation (equal); formal analysis (equal); investigation (equal); project administration (equal); visualization (equal); writing – original draft (equal). **Rein Posthuma:** Data curation (equal); investigation (equal); project administration (equal); writing – review and editing (equal). **Jorine E. Hartman:** Conceptualization (equal); funding acquisition (equal); investigation (equal); writing – review and editing (equal). **Hester van der Vaart:** Conceptualization (equal); project administration (equal); writing – review and editing (equal). **Eline bij de Vaate:** Project administration (equal); writing – review and editing (equal). **Anouk W. Vaes:** Investigation (equal); project administration (equal); writing – review and editing (equal). **Bram van den Borst:** Project administration (equal); writing – review and editing (equal). **Dirk van Ranst:** Project administration (equal); writing – review and editing (equal). **Martijn A. Spruit:** Project administration (equal); writing – review and editing (equal). **Lowie E. G. W. Vanfleteren:** Conceptualization (equal); funding acquisition (equal); writing – review and editing (equal). **Dirk-Jan Slebos:** Conceptualization (equal); funding acquisition (equal); writing – review and editing (equal).

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CONFLICT OF INTEREST STATEMENT

BvdB reports consulting fees from Boehringer Ingelheim bv (Payments made to my institution, outside the submitted work), and payments or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Boehringer Ingelheim bv and Genzyme Europe bv (Payments made to my institution, outside the submitted work) and support for attending meetings and/or travel from Chiesi Pharmaceuticals bv (Payments made to my institution, outside the submitted work). MAS reports all support for the present manuscript from The Netherlands Lung Foundation (all paid to the institution), grants or contracts from Netherlands Lung foundation, Stichting Astma

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DATA AVAILABILITY STATEMENT

Marieke C. van der Molen had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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HUMAN ETHICS APPROVAL DECLARATION

The study was approved by the ethics committees of the University Medical Center Groningen, the Netherlands, and Ciro, Horn, the Netherlands (METc 2018/241) and written informed consent was obtained from all subjects.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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