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Early View

Original research article

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The impact of endoscopic lung volume reduction on physical activity coaching in patients with severe emphysema

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Take home message:

Endoscopic lung volume reduction for patients with severe emphysema is not a prerequisite for physical activity coaching to successfully increase daily physical activities, although it might alleviate patients' experienced difficulties with physical activity.

Word count: 2408 words

Keywords: chronic obstructive pulmonary disease; emphysema; lung volume reduction; physical activity; coaching

Abstract

Introduction

Endoscopic lung volume reduction (ELVR) aims to improve pulmonary function in severe emphysema. Physical activity (PA) coaching is expected to improve daily life PA. When improving ventilatory constrains in severe COPD, a better response to PA coaching is expected. The present study investigated the impact of PA coaching in addition to ELVR in severe emphysema.

Methods

Patients allocated, based on fissure integrity, in the ELVR or no-ELVR cohort, received the PA coaching intervention with a step counter and smartphone application from 3 to 6 months follow-up. The primary endpoint of this research question was the change in daily step count from baseline to 6 months follow-up compared between the ELVR and no-ELVR cohort. The secondary endpoints were time spent in moderate to vigorous PA, movement intensity, and patient-reported experience with PA between ELVR and no-ELVR.

Results

At 6 months, PA in both ELVR+coaching (1479±460 steps/day; p=0.001) and no-ELVR+coaching (1910±663 steps/day; p=0.004) improved within group, without significant between group differences (-405±781 steps/day; p=0.60). Patients in the ELVR group tended to experience less difficulty with PA compared to no-ELVR+coaching (7±4 points, p=0.08).

Conclusion

We found that physical activity coaching is feasible and can help to enhance physical activity in patients with severe emphysema. Improving the ventilatory capacity through endoscopic lung volume reduction is not a prerequisite for a successful coaching intervention to increase objectively measured physical activity, although it alleviates patients' experienced difficulty with physical activity in patients with severe COPD.

Main paper

Introduction

Patients with end-stage chronic obstructive pulmonary disease (COPD) have severely reduced ventilatory capacity resulting in dyspnea (1) and decreased daily life activity (2). In those patients, as in the general population, physical activity (PA) has important health benefits, lowers mortality risk, and should therefore be encouraged as part of the management (1).

Physical inactivity is embedded in the dyspnea-inactivity vicious circle and is mainly driven by airflow limitation, lung hyperinflation and COPD exacerbations (3). Different interventions including optimal pharmacotherapy, pulmonary rehabilitation and physical activity coaching can be offered to alleviate symptoms and improve health. Physical activity coaching interventions were effective in enhancing PA in this patient population (4, 5). Findings of the PROactive consortium showed a significant effect of a 3-month tele coaching intervention on PA by using a step counter and a smartphone application which was based on important principles of behaviour change to improve daily life activity (6, 7). Sub-analyses revealed a smaller effect of the tele coaching intervention in patients with lower exercise capacity and higher dyspnea scores.

Surgical or endoscopic lung volume reduction is a treatment option for a selected group of symptomatic COPD patients with severe emphysema and hyperinflation (8). The aim of lung volume reduction is to improve airflow obstruction, decrease hyperinflation and thereby improve ventilatory capacity and symptoms of dyspnea (9-11). Becoming less invasive, endoscopic lung volume reduction (ELVR) has rapidly grown in popularity. By first improving symptoms of dyspnea and diminishing the burden of being active with ELVR, a better response to PA coaching programs in improving daily life activity could be expected.

We hypothesize that patients, who undergo ELVR followed by a PA coaching intervention, will have a larger improvement of daily PA as compared to patients who do not undergo ELVR prior to PA coaching. To investigate this hypothesis, the current study compared the response of adding a 3 months PA coaching program to patients allocated to an ELVR intervention (ELVR+coaching) versus patients not eligible for ELVR (no-ELVR+coaching).

Methods

Subjects

The present study reports a secondary research question embedded in the Belgian Endobronchial Valve Study (BEVA study, NCT03264768) (12). Patients were enrolled in this study between July 2017 and February 2020. All subjects were screened and discussed at a multidisciplinary emphysema expert meeting (MEET). Subjects meeting the eligibility criteria were invited for the study and signed informed consent. Details on the MEET, inclusion criteria, ELVR intervention and its effectiveness were described elsewhere (12). In summary, patients with severe heterogeneous emphysema, a six-minute walk distance (6MWD) between 100 and 450 meter and modified Medical Research Council (mMRC) score ≥ 2 were included in the trial (table S1). The study was approved by the local Ethical Committee UZ / KU Leuven (study ID s60207).

Design

This is a single centre, prospective interventional cohort trial. Subjects with complete fissure integrity were selected for endoscopic lung volume reduction (ELVR group), subjects with incomplete fissures were allocated to the no-ELVR group. Subject allocation was performed blinded for PA outcomes. All subjects were followed-up for 6 months and PA coaching was provided in both cohorts after 3 months of follow-up (Figure 1).

The study consists of three evaluation moments: 1) baseline visit; 2) intermediate follow-up visit at 3 months (= start of the PA coaching intervention); 3) final follow-up visit at 6 months (= end of the PA coaching intervention).

Physical activity coaching intervention

The PA coaching intervention was provided for three months to all subjects, as part of our emphysema care program, and started three months after group allocation. Subjects were provided with a waist-worn step counter and a project-tailored smartphone application (Linkcare, Barcelona, Spain).

An individualized step goal was determined and patients received direct feedback on daily step counts. The patient received daily and weekly feedback on the step goal through the smartphone application. Once a week, subjects were encouraged through the coaching application to increase their daily step goal for the upcoming week. The coach had access to the step count data through an online platform, and phone contacts were set in case the patients did not reach the step goal, did not want to increase the step goal or were not compliant with transferring the step count data to the smartphone application. Detailed information on the PA coaching and its standardisation is described by Demeyer, et al. (6).

Physical activity outcomes

The primary endpoint for this research question was the change in mean daily step count from baseline to 6 months follow-up, objectively measured by the Dynaport MoveMonitor (DAM, McRoberts, The Hague, the Netherlands) (13). Movement intensity (expressed as m/s^2) and time spent in moderate to vigorous intense activities (expressed as minutes per day) were retrieved as secondary endpoints. Patients were instructed to wear the DAM on the lower back for 7 consecutive days during awake hours, except during washing or bathing. A valid measurement was qualified as at least 2 weekdays with at least 8 hours of wearing time. Weekend days were excluded from the analyses (14).

Patients simultaneously wore an Actigraph GT3X (applied to the same strap) as back-up PA measurement, used for multiple imputation of daily step count in case of failed Dynaport measurement (details described in supplement S4-5) (13).

Secondary outcomes

The following outcomes were measured at each clinical visit: (i) patients' reported experience of PA by the clinical visit-PROactive Physical Activity in COPD (C-PPAC) instrument, which captures experienced amount of PA and experienced difficulty with PA (15, 16); (ii) exercise capacity by the best out of two 6-minute walk tests (6MWT) according to ERS-ATS guidelines in a corridor of 50m (17); (iii) pulmonary function test (including post-bronchodilator spirometry, bodyplethysmography and diffusion capacity) according to ATS-ERS guidelines (18); and (iv) quality of life and symptoms of dyspnea by the Saint George Respiratory Questionnaire (SGRQ) (19) and mMRC dyspnea scale (20).

Statistics

The Belgian Endobronchial Valve Study was powered on the improvement in post-bronchodilator FEV_1 at 3 months (12). No a-priori sample size calculation was performed for the PA secondary outcomes.

To test the primary aim of this manuscript (i.e. change in main daily step count from baseline to 6 months FU between 'ELVR+coaching' versus 'no-ELVR+coaching'), between group differences at 6 months were analysed using mixed model repeated measures analyses, with mean step count as dependent and intervention and visit (both as class variables) as independent variables. We retrieved the intervention*visit interaction effect as main result. Within group changes over time were investigated by separate mixed model repeated measures analyses retrieving the time effect.

A responder analysis was performed for changes in daily step count and C-PPAC using chi-square tests. The minimal important difference (MCID) was set at 1000 steps per day for mean step count

(21), at 6 points for the C-PPAC total score, and at 4 points for the C-PPAC difficulty and amount sub score (16).

An association between changes in PA from 0 to 6 months and possible determinants (exercise capacity and pulmonary function) was explored by general linear models (with change in step count from baseline to 6 months follow-up as the dependent variable, and possible determinants categorized according to tertiles as independent variables). The investigated outcomes were: 1) FEV_1, RV, RV/TLC and 6MWD at 3 months follow-up (i.e. before the start of the coaching intervention); and 2) the change between baseline and 3 months follow-up for FEV_1, RV, RV/TLC and 6MWD. Data of the two cohorts (ELVR and no-ELVR) were pooled to create tertiles. These single exposure models were adjusted for baseline step count.

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina, USA). P-value lower than 0.05 was interpreted as statistically significant for all analyses. Data are presented as mean and standard deviation (SD), standard error (SEM) or proportions. All patients were included in the current analysis, even if they did not complete the 3 months PA coaching program.

Results

Study population

All patients followed the BEVA study design. Inclusions were stopped when endobronchial valve treatment was reimbursed in Belgium and became part of clinical routine care (February 2020). Fifty-six subjects signed informed consent and 51 patients were allocated (Figure 2). Based on Chartis assessment, 28 patients were treated with endobronchial valves and 23 patients were followed-up in the no-ELVR group. PA coaching was provided to all patients. Two patients in the no-ELVR group were not willing to start the coaching and three subjects in the ELVR group did not complete the coaching intervention. Baseline characteristics of ELVR and no-ELVR cohorts are described in table 1. Patients were very inactive at baseline (mean±SEM for respectively ELVR and no-ELVR: 4178±297 and 4034±399 steps per day, p=0.82).

Outcomes on physical activity

PA coaching significantly improved within group daily step count at 6 months in both the ELVR+coaching (1479±460 steps per day, p = 0.001) and the no-ELVR+coaching group (1910±663 steps per day, p = 0.004). No differences were observed between groups (-405 ± 781 steps per day; p

= 0.60). Similar observations were made for time spent in moderate to vigorous intense activities (MVPA) and movement intensity at 6 months follow-up (table 2 and figure 3). A trend towards lower C-PPAC score for difficulty with PA was observed favouring ELVR (between group difference at 6 months 7 ± 4 points in favour or ELVR+coaching, p = 0.08) (table 2 and figure 3).

In terms of steps per day, 52% of the patients in the ELVR+coaching and 42% of patients in the no-ELVR+coaching group responded to the coaching intervention (p=0.51 between groups). A significant higher proportion of subjects reached the predefined MCID for the C-PPAC difficulty score in ELVR+coaching compared to no-ELVR+coaching at 6 months (response rate 67% versus 29%, respectively, p=0.02).

Exploratory analysis: determinants of successful PA coaching intervention

Figure 4 shows the determinants for successful coaching. Better FEV_1 (p=0.06) and less hyperinflation (i.e. reduced RV/TLC) (p=0.04) tended to be associated to a better response to coaching, but RV and 6MWD at 3 months were not (resp. p=0.32; p=0.45). Changes in FEV_1, RV, RV/TLC ratio and 6MWD (0-3 months) were not related to coaching response (p>0.05 for all).

Discussion

This study shows that PA can be improved in patients with severe emphysema using PA coaching, regardless of undergoing ELVR or not. Current data do not confirm our hypothesis that improved dyspnea and better function after ELVR yields a better response in PA coaching compared to more symptomatic or more ventilatory-limited patients without ELVR. Patients in the ELVR group did experience less difficulty with PA compared to patients without ELVR.

This research illustrates that the PA coaching intervention is feasible and may help to improve PA, even in patients with severe COPD. In contrast to our initial hypothesis, our findings demonstrate that clinical significant improvements by lung volume reduction are no prerequisite for a successful PA coaching program. Nevertheless, our exploratory analysis on determinants of change in PA suggests that the PA coaching benefits may be larger in patients with a better lung function at the start of the coaching intervention. These findings corroborate with earlier studies (6), and are to some extent confirmed by the Physacto study where an increase in PA was also achieved in the group treated with a placebo bronchodilator (22). Of note, the patients in 'Physacto' had substantially more ventilatory reserve compared to our patient group.

A trend towards significant difference between the ELVR and no-ELVR group was found in C-PPAC score for experienced difficulty with PA at 6 months. Patients undergoing ELVR+coaching were 2.3 times (95%CI: 1.13-5.2) more likely to improve experienced difficulty with PA compared to usual care without ELVR. This finding suggests that ELVR tends to alleviate difficulties during daily life activities. Again, these data are in line with the Physacto trial in which the addition of bronchodilator therapy to behavioral intervention could not further improve the objectively measured daily life activity, but did significantly affect the perceived difficulty with PA (22). Interventions such as bronchodilator therapy or ELVR can both improve experienced difficulty with PA. It is tempting to speculate that this improvement is important to maintain daily life activities on the long term or to slow down the expected decline in PA. This still needs to be confirmed with long-term follow-up data.

Additionally, our data show that ELVR as stand-alone intervention is not enough to significantly change daily life activities in patients with end-stage COPD. ELVR provides physiological improvements to patients with severe emphysema, but this results in only limited natural recovery of PA outcomes 3 months after the intervention. This is in contrast to results of Hartman, et al. showing a significant improvement of 1252±1468 mean steps/day 6 months post ELVR without any additional intervention (23). Baseline characteristics for lung function, exercise capacity and PA were comparable between both studies, but it is difficult to address if a difference in encouragement or education about PA can explain these findings.

Strengths and limitations

This study design allows us to investigate how important improvements in ventilatory constrains and functional capacity determine the response to PA coaching. By including objectively measured PA as well as subjectively measured patients' perception on daily life activities, we provide a holistic exploration of physical activity. With a complex study design and no randomization, we have to recognize a number of limitations. First, as this pre-planned study was part of a larger trial at University Hospitals Leuven (BEVA study), the original sample size calculation was powered for change in FEV_1 at 3 months follow-up, and not powered for objectively measured PA. However, a convenient sample size in both the ELVR and no-ELVR group was achieved. Second, in our study, PA coaching was offered after 3 months post intervention, however, the ideal timing of this intervention after ELVR is still a matter of debate. As PA coaching was implemented between 3 and 6 months follow-up, the observed benefits on PA may still relate to the long-term benefits of the ELVR intervention. The observation of PA improvements in the no-ELVR group occurring when coaching was implemented, however, is indicative of the power of such a behavioral intervention. Finally, patients included in this experimental study were highly motivated and compliant, which might not

be representative for the complete COPD population. This could have had an impact on the PA coaching program.

Conclusion

Physical activity coaching is feasible and can help to enhance physical activity in patients with severe emphysema. Improving the ventilatory capacity through lung volume reduction is not a prerequisite for successful PA coaching in patients with severe emphysema, although it alleviates patients' experienced difficulties with PA.

Tables:

Table 1: Baseline demographics and clinical characteristics, expressed as mean ± SD or mean ± SEM(*) for ELVR group and no-ELVR group. *P* values for ELVR versus no-ELVR obtained by two-sample t-test and Fisher's exact test□.

Variable	ELVR group (n=28)	No-ELVR group (n=23)	*P*-value
Age (years)	64 ± 6	62 ± 6	0.21
Gender (% female)	44%	61%	0.40□
BMI (kg/m^2)	23 ± 3	22 ± 4	0.34
GOLD stage (% stage IV)	59%	48%	0.58□
FEV_1 (% of predicted)	31 ± 7	33 ± 7	0.41
RV (% of predicted)	223 ± 33	239 ± 49	0.17
RV/TLC	0.67 ± 0.06	0.64 ± 0.09	0.16
DLco (ml/min/mmHg)	2.74 ± 0.67	2.89 ± 0.88	0.50
6MWD (meter)	362 ± 72	377 ± 66	0.45
SGRQ total score	61 ± 10	62 ± 15	0.61
mMRC score			
2 (%)	22 %	30 %	0.37□
3 (%)	56 %	61 %	
4 (%)	22 %	9 %	
Mean steps per day (*)	4178 ± 297	4034 ± 399	0.82
MVPA	63 ± 37	65 ± 26	0.81
Movement intensity	1.60 ± 0.21	1.61 ± 0.22	0.79
C-PPAC total score	53 ± 10	52 ± 14	0.79
C-PPAC amount score	51 ± 14	50 ± 17	0.83
C-PPAC difficulty score	55 ± 9	54 ± 15	0.82

Definition of abbreviations: ELVR = endoscopic lung volume reduction; BMI = body mass index; GOLD: Global Initiative for Chronic Obstructive Lung Disease; FEV_1 = forced expiratory volume in one second; TLC = total lung capacity; RV = residual volume; 6MWD = six-minute walk distance; SGRQ = Saint George's Respiratory Questionnaire; MVPA = Moderate to vigorous intense physical activity; C-PPAC = clinical visit-PROactive Physical activity in COPD instrument.

Table 2: Changes for objectively measured physical activity and patient's perception of PA between ELVR versus no-ELVR at 6 months follow-up (between group differences) and within group changes at 3 and 6 months in both groups, expressed as mean±SEM; (*) indicates p-value of within group difference < 0.05.

		Within group difference 3 months	***Within group difference 6 months***	***Between group difference 6 months***	***Between group p value***
Mean daily steps (steps/day)	**ELVR**	545 ± 465	1479 ± 460 (*)	-404 ± 781	0.60
	no-ELVR	-23 ± 679	1910 ± 663 (*)		
MVPA (min/day)	**ELVR**	7 ± 8	15 ± 7 (*)	-3.22 ± 10	0.76
	no-ELVR	-0.7 ± 9	18 ± 7 (*)		
Movement intensity (m/s^2)	**ELVR**	0.02 ± 0.03	0.05 ± 0.03	-0.07 ± 0.05	0.20
	no-ELVR	0.03 ± 0.05	0.11 ± 0.04 (*)		
C-PPAC difficulty score (points)	**ELVR**	11 ± 3 (*)	11 ± 3 (*)	7.20 ± 4.10	0.08
	no-ELVR	-0.7 ± 3	3 ± 2		
C-PPAC amount score (points)	**ELVR**	3 ± 4	8 ± 4 (*)	0.74 ± 5.17	0.89
	no-ELVR	-0.1 ± 4	6 ± 3		
C-PPAC total score (points)	**ELVR**	7 ± 3 (*)	9 ± 3 (*)	4.23 ± 3.91	0.28
	no-ELVR	-2 ± 2	4 ± 2		

Figure 1: Design of the study. ELVR = endoscopic lung volume reduction; 0m = baseline visit; 3m FU = 3 months follow-up; 6m FU = 6 months follow-up.

Figure 2: Flowchart of the study. **Abbreviations**: ELVR = endoscopic lung volume reduction; CV = collateral ventilation; ITT = intention-to-treat; PA = physical activity, objectively measured; FU = follow up.

Figure 3: mean ± SEM for objectively measured physical activity and patient' perception of PA in patients with endoscopic LVR (black solid line) and no-ELVR (grey dotted line) at baseline, 3 months and 6 months post allocation. Physical activity coaching was provided in both groups between 3 and 6 months follow-up; indicated by light-grey bar. *: significant between-group differences for ELVR versus no-ELVR.

Figure 4: Association between lung function (FEV_1, RV, RV/TLC), exercise capacity (6MWD) obtained at 3 months follow-up and change in physical activity over 6 months. Pooled data from ELVR and no-ELVR categorized in tertiles (t1, t2, t3) from worse to better. Upper panel: determinants at 3 months follow-up – lower panel: change in determinants between baseline and 3 months follow-up. Range and sample size per tertile for all outcome measures are displayed in supplement (table S3).

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Conflict of interest: WJ reports a grant from PulmonX (for the endobronchial valves) and grants from AstraZeneca and Chiesi outside the submitted work. WJ is co-founder of ArtiQ, a KU Leuven spin-off company in respiratory diseases. No other competing interests were reported.

Contributors: WJ, TT, CD, GV DVR, JC and HD contributed to the study design and set-up of the protocol. AB, HD, LC, SE, HG, GV, DVR and CD contributed to the data collection. AB, HD, TT and WJ contributed to the data analyses and interpretation of the data. AB, HD, CD, TT and WJ contributed to the writing of the manuscript. All authors critically reviewed the manuscript. WJ is the guarantor of the study. All authors had full access to the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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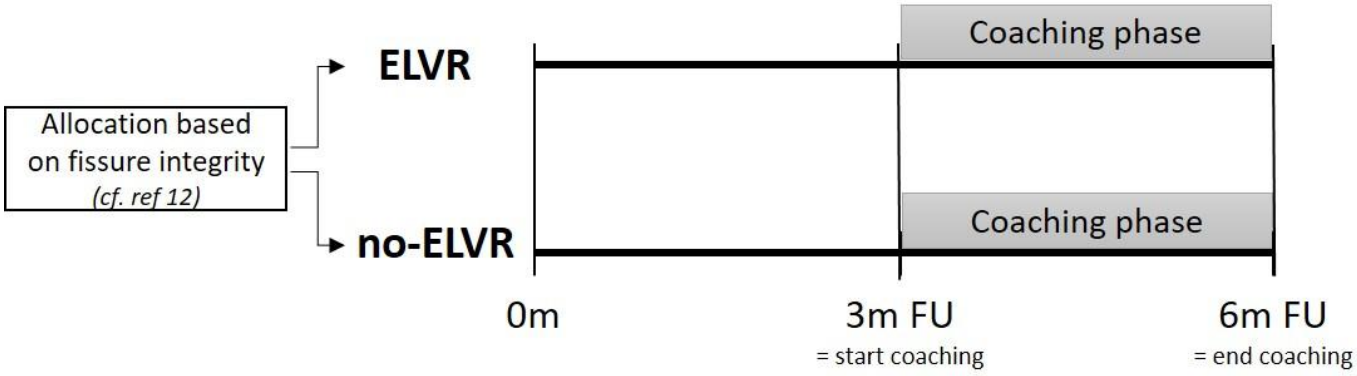
Allocation based
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ELVR
no-ELVR
Coaching phase
Coaching phase
0m
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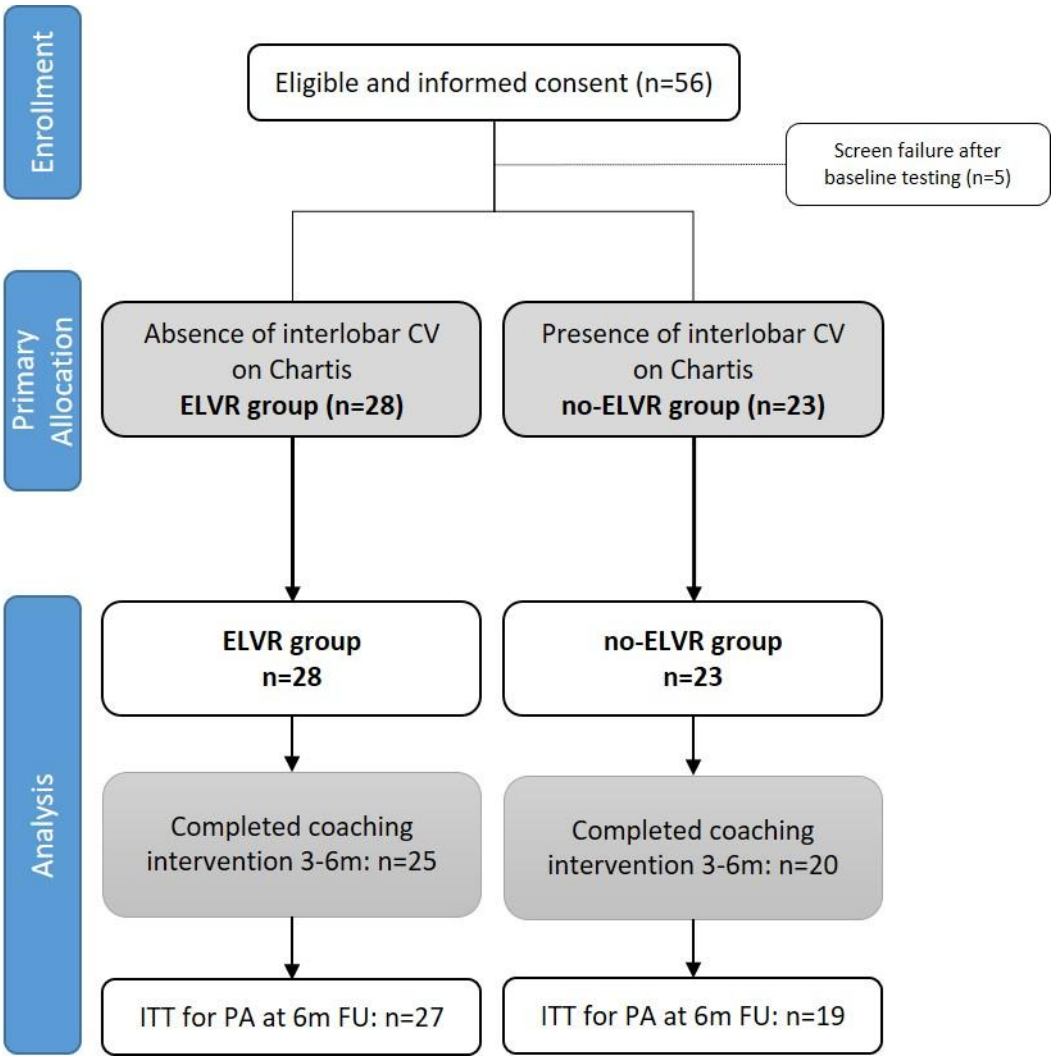
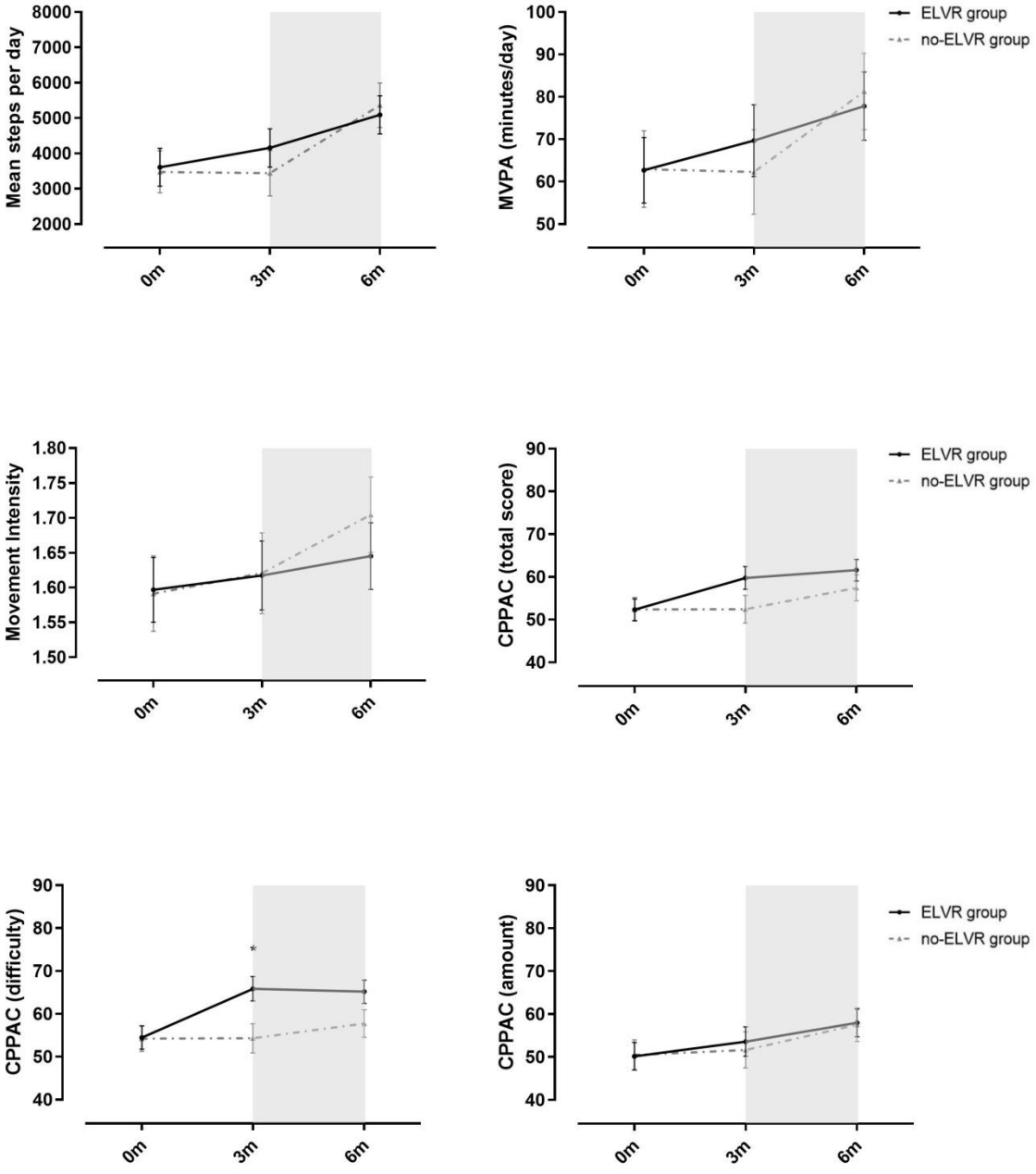
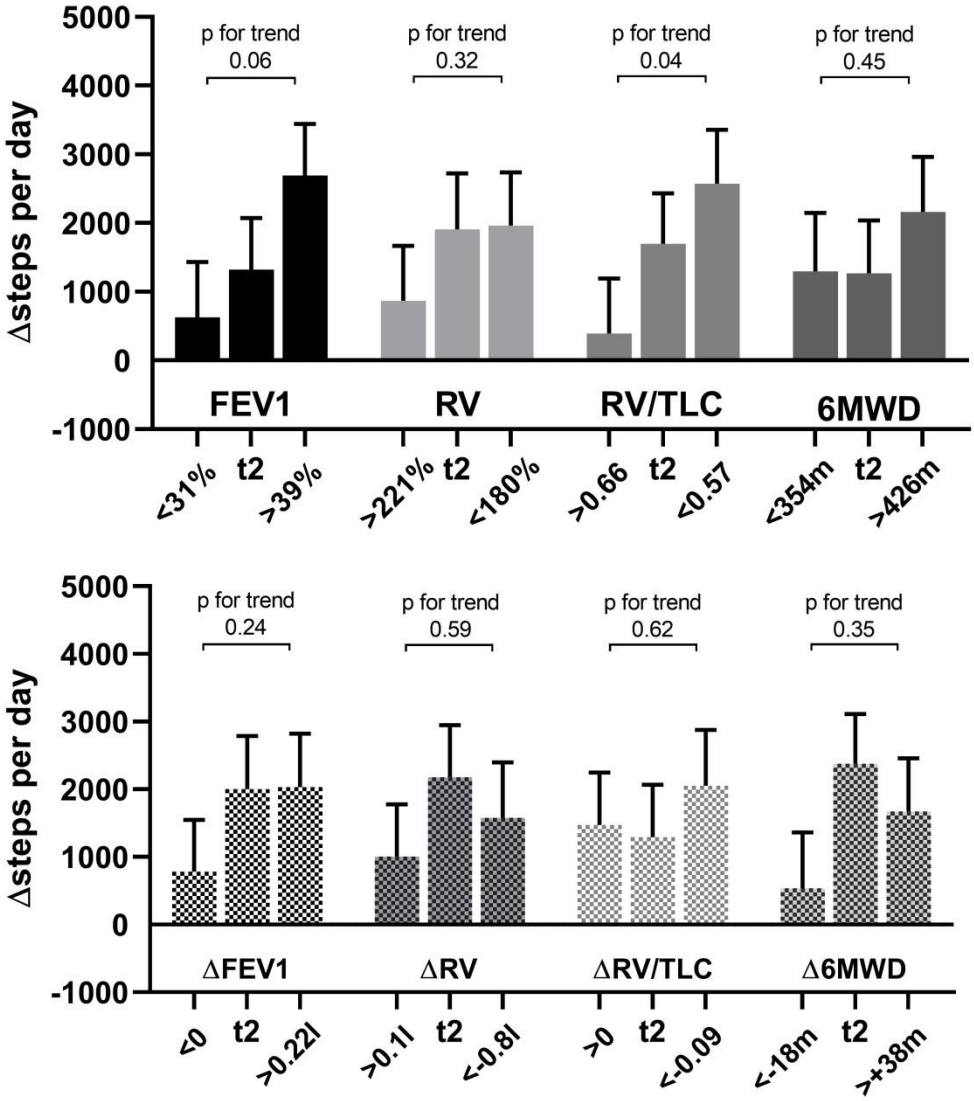
= start coaching
6m FU
= end coaching


Enrollment
Eligible and informed consent (n=56)
Screen failure after baseline testing (n=5)
Primary Allocation
Absence of interlobar CV on Chartis
ELVR group (n=28)
Presence of interlobar CV on Chartis
no-ELVR group (n=23)
Analysis
ELVR group n=28
no-ELVR group n=23
Completed coaching intervention 3-6m: n=25
Completed coaching intervention 3-6m: n=20
ITT for PA at 6m FU: n=27
ITT for PA at 6m FU: n=19


Mean steps per day
8000
7000
6000
5000
4000
3000
2000
0m
3m
6m
MVPA (minutes/day)
100
90
80
70
60
50
ELVR group
no-ELVR group
Movement Intensity
1.80
1.75
1.70
1.65
1.60
1.55
1.50
CPPAC (total score)
90
80
70
60
50
40
CPPAC (difficulty)
*
CPPAC (amount)


Δsteps per day
5000
4000
3000
2000
1000
0
-1000
p for trend
0.06
p for trend
0.32
p for trend
0.04
p for trend
0.45
FEV1
RV
RV/TLC
6MWD
<31%
t2
>39%
>221%
t2
<180%
>0.66
t2
<0.57
<354m
t2
>426m
Δsteps per day
5000
4000
3000
2000
1000
0
-1000
p for trend
0.24
p for trend
0.59
p for trend
0.62
p for trend
0.35
ΔFEV1
ΔRV
ΔRV/TLC
Δ6MWD
<0
t2
>0.22l
>0.1l
t2
<-0.8l
>0
t2
<-0.09
<-18m
t2
>+38m

Online Supplement:

Table S1: in- and exclusion criteria for enrolment in the main study.

Definition of abbreviations: FEV_1 = forced expiratory volume in one second; RV = residual volume; TLC = total lung capacity; TLCO = transfer factor of the lung for carbon monoxide; 6MWD = six-minute walk distance; mMRC = modified medical research counsil; LABA-LAMA = long-acting bronchodilator.

Inclusion criteria	Exclusion criteria
Age: 40 – 75 years old	Homogeneous emphysema on chest CT
Confluent, destructive heterogeneous emphysema on chest CT	PaCO2 > 60 mmHg or PaO2 < 45 mmHg with ambient air
Visual estimation of 70% complete fissure between target lobe and adjacent lobe on chest CT	Previous lung volume reduction surgery, lung transplantation or lobectomy
FEV1 < 60% predicted	TLCO or FEV1 < 20% predicted
RV > 150% predicted	Significant pulmonary hypertension (PaPsyst > 50 mmHg)
TLC > 90% predicted	Heart failure with ejected fraction < 40%
RV/TLC ratio ≥ 0.55	BODE index ≥ 7 and eligible for lung transplantation
6MWD < 450 meter	6MWD < 100 meter
mMRC score ≥ 2	Active cancer
LABA-LAMA bronchodilator therapy as minimum therapy	Life expectancy < 3 months
Smoking cessation > 6 months (proven by urinary cotinine levels)	Significant lung disease other than COPD or emphysema

Table S2: within group differences at 3 and 6 months follow-up and between group changes from baseline and 6 months follow-up for ELVR versus no-ELVR for secondary endpoints. Significant within group differences are indicates with *.

		WITHIN GROUP DIFFERENCE 3M	***WITHIN GROUP DIFFERENCE 6M***	***BETWEEN GROUP DIFFERENCE 6 MONTHS***	***BETWEEN GROUP P VALUE***
FEV1 (l)	**ELVR**	0.24 ± 0.03*	0.19 ± 0.03*	0.20 ± 0.05	<.0001
	no-ELVR	0 ± 0.03	-0.02 ± 0.03		
RV (l)	**ELVR**	-0.8 ± 0.13*	0.76 ± 0.14*	-0.84 ± 0.20	<.0001
	no-ELVR	-0.14 ± 0.15	0.08 ± 0.15		
6MWD (m)	**ELVR**	30 ± 12*	31 ± 12*	40.4 ± 16.6	0.02
	no-ELVR	-13 ± 10	-9 ± 10		
SRDQ total score (points)	**ELVR**	-16 ± 3.5*	-16 ± 3.5*	-13.40 ± 4.66	0.005
	no-ELVR	0.6 ± 2.7	-2.9 ± 2.7		
mMRC score (points)	**ELVR**	-0.86 ± 0.19*	-0.71 ± 0.20*	-0.36 ± 0.27	0.18
	no-ELVR	0.19 ± 0.17	-0.35 ± 0.17		

Table S3: determinants of change in physical activity: range of the tertiles and proportion of patients in each tertile.

Variabele	Tertile	Range (min ; max)	N ELVR group	N no-ELVR group
FEV1 3M %pred	t1	21 ; 31 %	5	11
	t2	31 ; 39 %	11	6
	t3	39 ; 72 %	12	4
ΔFEV1 (0-3M) (l)	t1	-0.25 ; 0.00 (l)	3	14
	t2	0.01 ; 0.21 (l)	10	5
	t3	0.22 ; 0.77 (l)	15	2
RV 3M %pred	t1	323 ; 221 %	3	13
	t2	218 ; 182 %	10	7
	t3	180 ; 119 %	15	1
ΔRV (0-3M) (l)	t1	0.7 ; -0.1 (l)	3	13
	t2	-0.1 ; -0.8 (l)	11	6
	t3	-0.8 ; -2.8 (l)	14	2
RV/TLC 3M	t1	0.78; 0.66	8	8
	t2	0.66; 0.57	9	8
	t3	0.57; 0.43	11	5
ΔRV/TLC (0-3M)	t1	+0.09; 0	4	15
	t2	0; -0.09	14	4
	t3	-0.09 ; -0.23	10	2
6MWT 3M (meter)	t1	212 ; 354 (m)	9	7
	t2	360 ; 419 (m)	8	9
	t3	426 ; 552 (m)	11	5
Δ6MWT (0-3M)	t1	-127 ; -18 (m)	7	9
	t2	-13 ; 37 (m)	8	9
	t3	38 ; 191 (m)	13	3

Supplement S4: Information on multiple imputation

Multiple imputation (by chain equation; n=20) was performed in case of missing step count values measured by DAM (n=123 measurement days). The imputation was based on available data of Actigraph monitor. If no Actigraph data was available, the imputation was not performed (only steps per day measured by Actigraph was used in the multiple imputation model, no additional variables were added). Multiple imputation was only performed for the primary endpoint (i.e. steps per day), not for any other PA outcomes. Non-imputed step count values are provided in table S8.

Table S5: mean steps count at baseline with and without multiple imputation

		Without multiple imputation	*With multiple imputation*
Mean steps per day at baseline - with weekend days	**ELVR**	3420 ± 445	4178 ± 297
	no-ELVR	3424 ± 359	4034 ± 399
Mean steps per day at baseline - without weekend days	**ELVR**	3610 ± 453	4317 ± 309
	no-ELVR	3638 ± 377	4149 ± 396