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CHAPTER

6

Improvement of physical activity after endobronchial valve treatment in patients with severe emphysema

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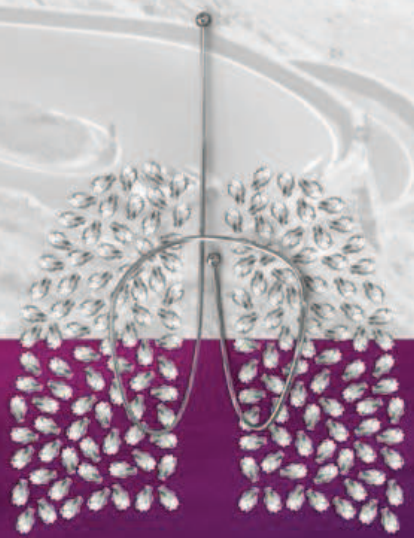

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ABSTRACT

Rationale
Bronchoscopic lung volume reduction using endobronchial valves is a promising treatment for severe emphysema patients without collateral ventilation. Physical activity is an important contributing factor for the autonomy of these patients.

Objective
We investigated the impact of endobronchial valve treatment on physical activity in patients with severe emphysema.

Methods
Physical activity was measured for 7 days by a triaxial accelerometer at baseline and 6 months follow-up after endobronchial valve treatment, and compared with standard medical care in a randomized controlled trial.

Results
Forty-three patients (77% female, age 59±9 years, FEV_1 30±7 % of the predicted value, steps 3563±2213 per day) wore the accelerometer and were included in the analysis. Nineteen patients received endobronchial valve treatment and 24 standard medical care. At baseline, physical activity level was comparable between groups.

After 6 months, the endobronchial valve group significantly improved compared to the controls in steps per day (+1252 versus -148) and locomotion time (+17 versus -2 minutes per day). Change in sit duration (0 versus +27 minutes per day) did not significantly differ.

Furthermore, a higher increase in steps per day was significantly associated with a stronger decrease in residual volume (r=-0.48) and a higher increase in FEV_1 (r=0.41) and in distance on 6 minute walk test (r=0.50).

Conclusion
Physical activity significantly improved after endobronchial valve treatment in patients with severe emphysema. This improvement was without any specific encouragement on physical activity.

INTRODUCTION

We recently showed that bronchoscopic lung volume reduction using endobronchial valves is a promising treatment modality targeting lung hyperinflation for patients with severe emphysema.[1] The results of this randomized controlled trial showed that endobronchial valve treatment significantly improved pulmonary function, exercise capacity and quality of life after 6 months in COPD patients characterized by emphysema and the absence of interlobar collateral ventilation.[1]

Potentially, the decrease in lung hyperinflation after endobronchial valve treatment could reduce dyspnea during exertion and consequently improve the functional capacity of the body. As dynamic and static lung hyperinflation are independent predictors of daily physical activity, especially in patients with advanced COPD,[2,3] endobronchial valve treatment could potentially improve the patient's physical activity level. A higher physical activity level in these patients may improve the patient's exercise capacity and lead to restoration of social participation and a more independent lifestyle. Contrary, in a pilot study we demonstrated that physical activity did not significantly improve after bronchoscopic lung volume reduction treatment.[4] However, this uncontrolled study had a small sample size and investigated the bronchoscopic lung volume reduction treatment with coils instead of endobronchial valves. To our knowledge, the effect of bronchoscopic lung volume reduction using endobronchial valves on daily physical activity was not investigated before.

Our aim was to investigate whether daily physical activity in patients with severe emphysema increases after a bronchoscopic lung volume reduction treatment using endobronchial valves.

METHODS

Study population and study design

A randomized controlled crossover trial investigating the endobronchial valve treatment was performed in the University Medical Center Groningen in The Netherlands between June 2011 and November 2014 (The STELVIO trial; Dutch trial register: NTR2876).[1] Patients with emphysema and a visually determinable treatment target on the CT scan and proven absence of collateral ventilation between the target lobe and adjacent lobe were included. The complete list of inclusion and exclusion criteria are listed in box 1. In total 68 patients were randomized, of which 34 patients received endobronchial valve treatment (EBV group), whereas 34 patients received standard medical care (control group). After 6 months, the control group also received the endobronchial valve treatment (crossover). During the study, physical activity was measured by an accelerometer for 7 days at baseline and for 7 days after 6 months follow up (post randomization and post crossover). The study was approved by the ethics committee of the University Medical Center Groningen, and all patients provided informed consent.

Box 1. The main inclusion and exclusion criteria.

Inclusion criteria

- Patient > 35 years of age
- CT scan indicates heterogeneous severe emphysema (i.e. based on visual assessment of a treatment target lobe)
- CT scan indicates intact fissures as assessed on the sagittal reconstructions of a thin slice CT scan
- Post-bronchodilator FEV_1 <60% of predicted value
- Post-bronchodilator total lung capacity>100% of predicted value and residual volume>150% of predicted value
- Dyspnea score of ≥2 on the mMRC scale of 0-4 (where higher scores indicate more severe emphysema)
- Patient has stopped smoking for a minimum of 6 months prior to entering the study
- Signed informed consent
- Subject is willing and able to comply with all study testing and procedures according to protocol and guidelines
- Lobar occlusion during endobronchial valve treatment achieved with study device (bronchoscopy required to assess eligibility)

Exclusion criteria

- Hypercapnia defined by $PaCO_2$>8.0 kPa, or hypoxemia defined by PaO_2<6.0kPa, both measured while breathing ambient air
- Distance on 6 minute walk test <140 meter
- Previous lung volume reduction surgery, lung transplantation or lobectomy
- Patient is on an antiplatelet agent (such as clopidogrel) or anticoagulant therapy (such as LMWH or coumarins) or has not been weaned off prior to procedure
- Involved in other pulmonary drug studies within 30 days prior to this study
- Evidence of other disease that may compromise survival, would interfere with completion of study, follow up assessments or that would adversely affect outcomes, such as lung cancer, and/or ASA class >III
- Evidence of collateral ventilation as measured with the Chartis system (bronchoscopy required to assess eligibility)

Measurements

All measurements were performed at baseline and after 6 months follow-up (post randomization and post crossover). Physical activity was measured by a triaxial accelerometer (DynaPort, McRoberts). The accelerometer was worn around the waist at the lower back. This accelerometer is a highly validated instrument for evaluating physical activity in patients with COPD.[5,6] Patients were instructed to wear the accelerometer for 7 days, day and night, except during showering and swimming. Lung function spirometry and body plethysmography were performed by blinded assessors (Jaeger MasterScreen™, CareFusion, Germany) according to the ATS/ERS guidelines.[7,8,9] Exercise capacity was measured by a 6 minute walk test according to the ATS guidelines.[10] Quality of life was measured by the St. George's Respiratory Questionnaire.[11] Dyspnea severity was measured by the modified Medical Research Council (mMRC) scale.[12]

Statistical analyses

Patients were included in the analyses if they had worn the accelerometer for at least 4 full days per assessment, in accordance with literature.[13] A day was considered a valid measurement day if the device was worn for at least 94% of the day.[14] When patients did not want to wear the accelerometer during the night, this time was recorded as lying. Furthermore, to be included in the analyses the patient had to wear the accelerometer for at least 2 times; at baseline and after 6 months follow-up. Differences between EBV group and control group were tested with an independent-samples t-test. Baseline and 6 months follow up measurements were compared with a paired-samples t-test or Wilcoxon signed-rank test. Pearson correlation coefficients were calculated to test univariate associations between physical activity parameters and other clinical parameters. P-values below 0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics version 22.

RESULTS

Participants

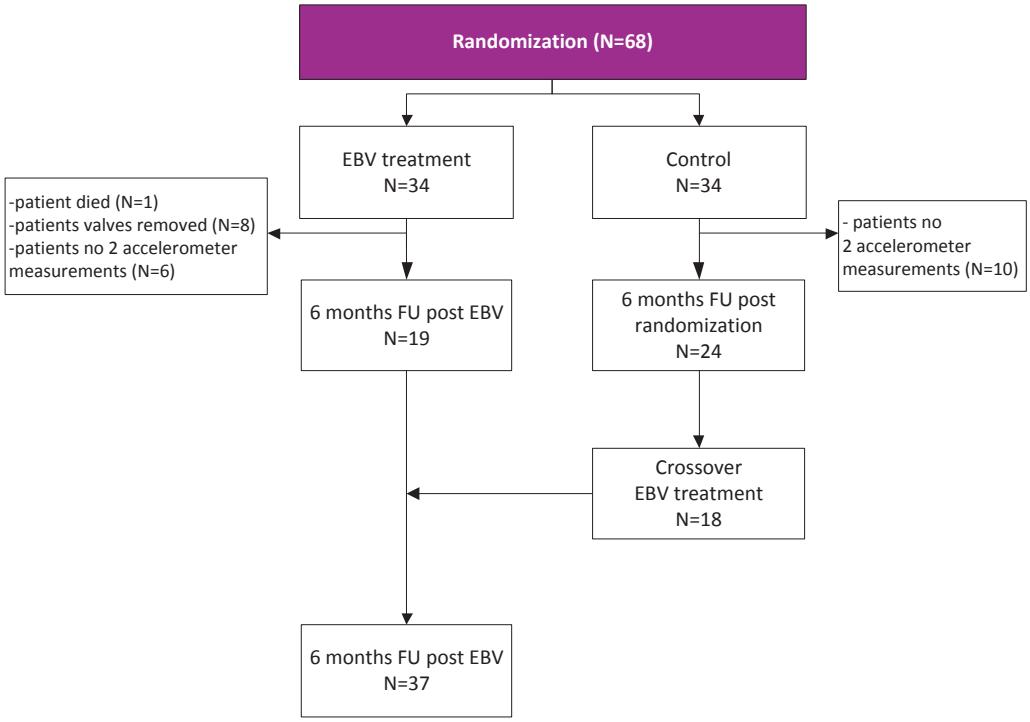
Characteristics of the 43 patients who had evaluable accelerometer data are shown in table 1 and the flow of patients through the study is shown in figure 1. Of these 43 patients, 19 patients were treated with the endobronchial valve treatment and 24 patients received standard medical care. No significant differences in clinical characteristics were found between the EBV group and control group at baseline. After crossover of the control group, 18 patients also wore the accelerometer 6 months after crossover, leading to 37 patients with evaluable 6 months post endobronchial valve treatment data.

Table 1. Patient characteristics (N=43).

Characteristic	
Male/Female, N	10/33
Age, years	59±9
BMI, kg/m2	24.8±4.3
FEV_1, % of predicted value	30.0±7.4
FVC, % of predicted value	79.0±16.6
RV, % of predicted value	215±31
Ratio of RV to TLC, %	59.5±8.1
Oxygen saturation, %	94 (88-98)
mMRC, score	2.4±0.6
SGRQ, total score	56.3±12.7
EQ5D, VAS score	52.4±15.8
CCQ, total score	2.6±0.6
Distance on 6 minute walk test, meter	378±77
Steps, mean per day	3055 (714-11352)
Locomotion duration, % per day	4.6±2.4
Sit duration, % per day	39.5±9.0
Inactivity duration, % per day	83.0±5.8
Physiotherapist training ≥ 2 per week, N (%)	29 (67%)

Data are presented as N (%), mean ± standard deviation or median (range). BMI: Body mass index; FEV_1: Forced Expiratory Volume in 1 second, FVC: Forced vital capacity, RV: Residual volume, TLC: Total lung capacity, mMRC: medical Modified Research Council, SGRQ: St. George's Respiratory Questionnaire, EQ5D: EuroQol 5D questionnaire; CCQ: Clinical COPD Questionnaire.

Figure 1. Flowchart of participant flow through the study.



Endobronchial valve treatment (N=19) compared to controls (N=24)

The differences between the EBV group and control group in change in physical activity and other clinical parameters between baseline and 6 months follow up are shown in table 2 and figure 2. The EBV group significantly improved compared to the control group in mean steps per day (+1252 versus -148), locomotion duration (+17 versus -2 minute per day) and locomotion intensity (+4.6 versus -1.5% change compared to baseline). The change in sitting duration (0 versus +27 minute per day) and inactivity duration (-16 versus +6 minute per day) did not differ significantly between groups. Furthermore, the EBV group significantly improved in spirometry results (FEV_1 and forced vital capacity), static hyperinflation (residual volume), dyspnea severity, quality of life and exercise capacity compared to the control group.

Endobronchial valve treatment including crossover (N=37)

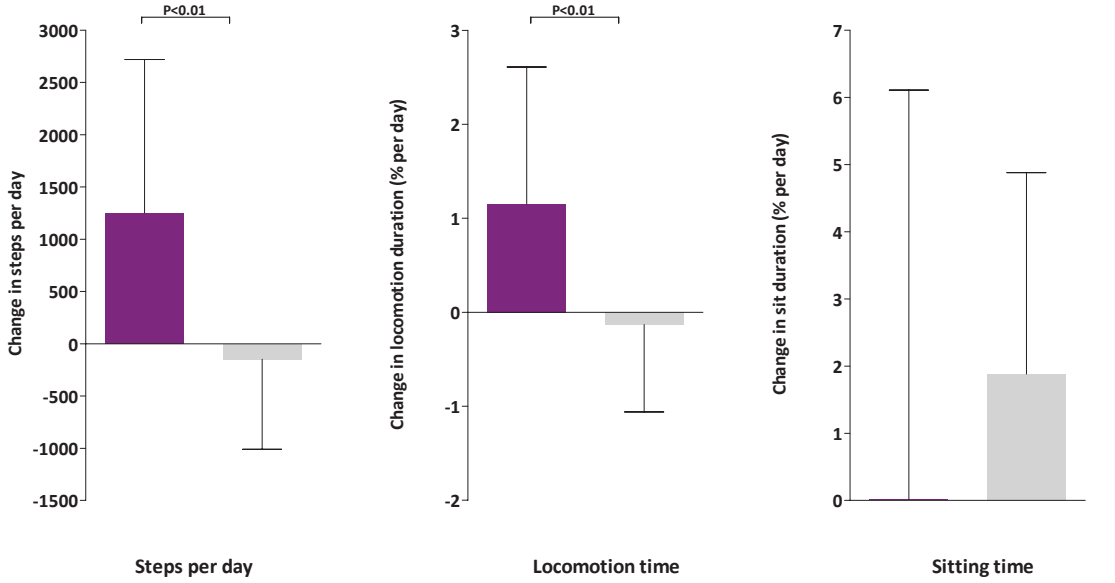
The changes in physical activity and other parameters between baseline and 6 months follow up including the crossover patients are shown in table 3. The individual patient data of the change in steps per day is shown in figure 3. After endobronchial valve treatment patients significantly improved compared to baseline in steps per day (mean +1133, 95%CI 711-1556), locomotion duration (mean +16, 95%CI 9.3-21.9 minute per day) and locomotion intensity (+3.1% change compared to baseline). Sitting duration (mean -10.5, 95%CI -36.5; 15.6 minute per day) and inactivity duration (mean -16.2, 95%CI -39.6; 7.3 minute per day) did not significantly change 6 months after endobronchial valve treatment.

Table 2. Difference between EBV treatment group and control group in change in physical activity and other clinical characteristics at 6 months FU.

	EBV group (N=19)		Control group (N=24)		Between group	
	absolute	relative (%)	absolute	relative (%)	difference	P value
Physical activity						
Steps, per day	1252±1468	57.1±73.3	-148±862	-1.2±18.8	1340±380	0.001
Locomotion duration, % per day	1.15±1.46	36.4±49.7	-0.13±0.93	-1.6±16.6	1.28±0.37	0.001
Sit duration, % per day	0.01±6.1	1.44±19.0	1.88±3.0	5.22±8.2	-1.86±1.52	0.230
Inactivity duration, minute per day	-1.1±3.2	-1.3±3.9	0.39±3.0	0.62±3.65	-1.49±0.95	0.126
Lung function						
FEV_1, % of predicted value	7.7±5.6	28.2±24.8	1.1±3.5	3.9±11.3	6.7±1.5	<0.001
FVC, % of predicted value	18.3±15.5	25.0±25.4	2.4±11.3	4.0±14.5	21.0±6.2	<0.001
RV, % of predicted value	-43.8±25.9	-20.8±11.5	-2.5±13.3	-0.8±6.0	-41.3±6.5	<0.001
Quality of life						
mMRC, score	-0.58±0.69	-21.9±24.9	-0.04±0.46	-0.69±17.4	-0.54±0.18	0.007
SGRQ, total score	-15.7±16.3	-27.6±28.0	-3.0±9.1	-3.7±13.7	-12.7±4.2	0.005
Distance on 6 minute walk test, m	84.5±62.1	26.4±22.0	-19.5±35.4	-5.1±10.4	104.0±16.3	<0.001

Data are presented as mean ± standard deviation. Δ absolute change: absolute change between 6 months follow up and baseline, Δ % change: relative change between 6 months follow up and baseline, g: average body acceleration. Difference between groups in Δ absolute change were tested with an independent-samples t-test. FEV_1: Forced Expiratory Volume in 1 second, FVC: Forced vital capacity, RV: Residual volume, mMRC: medical Modified Research Council, SGRQ: St. George's Respiratory Questionnaire

Figure 2. Change between baseline and 6 months follow up in steps per day, locomotion time and sitting time in EBV group and the control group. Bars represent means and whiskers represents standard deviations.



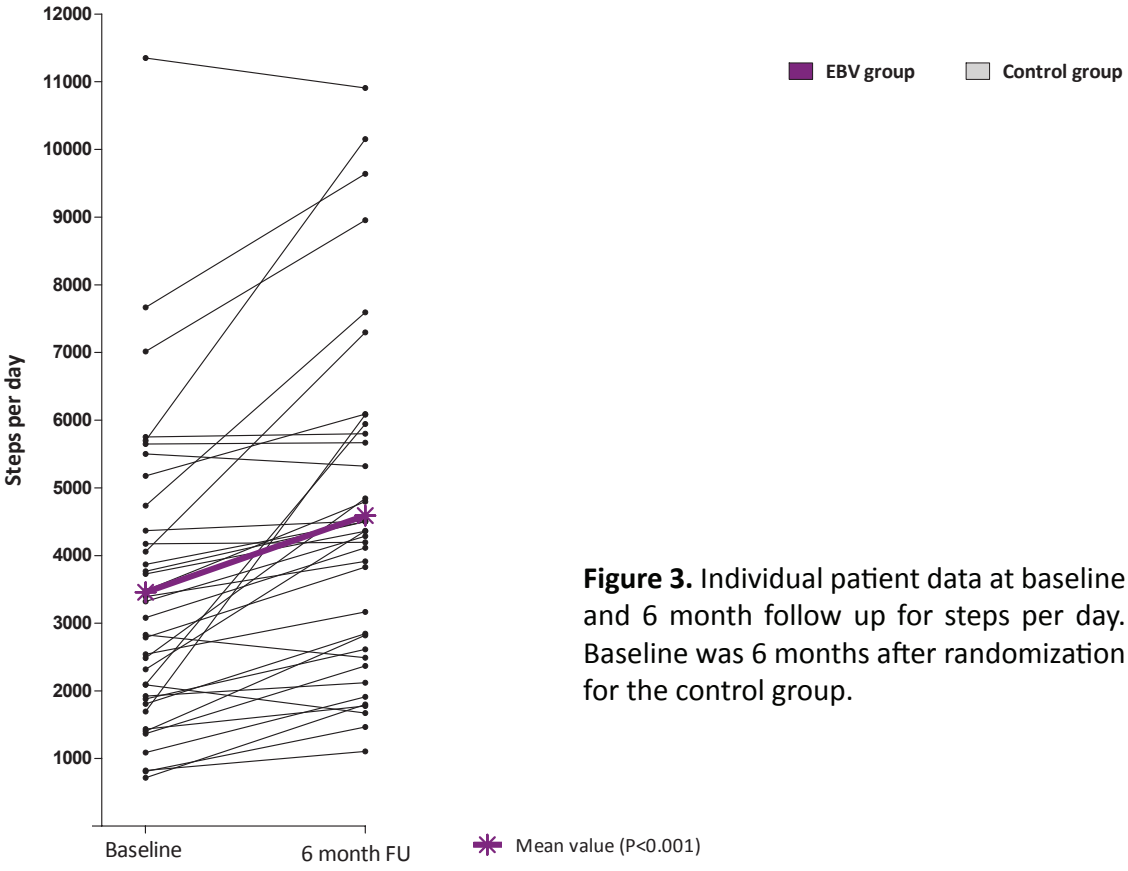


Figure 3. Individual patient data at baseline and 6 month follow up for steps per day. Baseline was 6 months after randomization for the control group.

Table 3. Change in clinical characteristics at 6 months after endobronchial valve treatment (N=37).

	baseline	6 months of follow up	P value	relative change
Physical activity				
Steps, per day	3456±2216	4589±2493	<0.001	47.5±56.9%
Locomotion duration, % per day	4.6±2.5	5.6±2.6	<0.001	34.4±41.8%
Sitting duration, % per day	40.9±9.2	40.2±9.8	0.421	-1.1±15.7%
Inactivity duration, minute per day	83.1±5.4	82.0±7.1	0.171	-1.3±6.0%
Lung function				
FEV_1, % of predicted value	31.1±7.8	38.4±8.8	<0.001	25.6±21.3%
FVC, % of predicted value	80 (54-110)	96 (57-135)	<0.001*	17.6 (-15-58)%
RV, % of predicted value	216 (161-273)	170 (108-251)	<0.001*	-18.0 (-44.7-5.48)%
Quality of life				
mMRC, score	2.5±0.65	2.0±0.65	<0.001	-16.9±21.9%
SGRQ, total score	54.2±10.3	40.1±15.8	<0.001	-24.9±26.6%
Distance on 6 minute walk test, m	366±82	433±74	<0.001	21.3±18.6%

Data are presented as mean ± standard deviation or median (range). Differences between baseline and 6 months follow up were tested with a paired-samples t-test or *Wilcoxon signed rank test. Δ relative change: relative (%) change between baseline and 6 months follow up.FEV_1: forced expiratory volume in 1 second, FVC: forced vital capacity, RV: residual volume, mMRC: modified Medical Research council scale, SGRQ: St. George's respiratory questionnaire, 6MWD: 6 minute walk distance.

Association between physical activity and other clinical variables.
The univariate associations between physical activity parameters and other clinical variables are shown in table 4. In the population including the EBV group and control group (N=43) change in steps per day between 6 months follow up and baseline was significantly (P<0.05) associated with change in residual volume (rho= -0.48), change in FEV_1 (rho=0.41), change in distance on 6 minute walk test (rho=0.50) and change in SGRQ (rho= -0.41), but not with change in mMRC. In the population including the EBV group and crossover EBV group (N=37) change in steps per day was not significantly associated with change in other clinical variables. In these patients, at 6 months follow up, steps per day was significantly associated with FEV_1 (rho=0.54), distance on 6 minute walk test (rho=0.61), SGRQ (rho=-0.34) and mMRC (rho=-0.59) but not with residual volume.

Table 4. Univariate associations between physical activity parameters and clinical parameters.

A. EBV group and control group (N=43)

	Δ steps per day	Δ movement intensity	Δ sitting time
Δ RV, Liter	**-0.478**	**-0.370**	0.179
Δ FEV_1, Liter	**0.411**	**0.348**	**-0.354**
Δ 6MWD, meter	**0.503**	**0.605**	-0.257
Δ SGRQ, total score	**-0.412**	-0.204	0.189
Δ mMRC, score	-0.181	-0.124	0.101

B. EBV group + crossover EBV (N=37): change between baseline and 6 months FU

	Δ steps per day	Δ movement intensity	Δ sitting time
Δ RV, Liter	-0.085	-0.253	0.189
Δ FEV_1, Liter	0.056	0.134	-0.136
Δ 6MWD, meter	0.161	**0.426**	0.007
Δ SGRQ, total score	-0.243	-0.100	0.209
Δ mMRC, score	-0.178	-0.156	0.052

C. EBV group + crossover EBV (N=37): 6 months FU

	Δ steps per day	Δ movement intensity	Δ sitting time
RV, Liter	-0.096	-0.099	0.004
FEV_1, Liter	**0.540**	0.281	**-0.441**
6MWD, meter	**0.611**	**0.378**	**-0.764**
SGRQ, total score	**-0.340**	-0.161	**0.408**
mMRC, score	**-0.593**	**-0.365**	**0.471**

DISCUSSION

To our knowledge, this was the first study that measured physical activity before and after endobronchial valve treatment in patients with severe COPD. Our results showed that physical activity significantly improved 6 months after endobronchial valve treatment with a difference in improvement in physical activity by 1340 steps per day between the EBV group and the control group.

In contrast to the pilot study with coils,[4] the current study did demonstrate significant improvements in daily physical activity after treatment with endobronchial valves. The pilot study investigating the coil treatment was uncontrolled and had a small sample size (N=14) and the number of steps only increased on average 400 steps per day 6 months after the treatment. The reason for this difference could be a less effective treatment as also the changes in other clinical parameters, like lung hyperinflation and exercise capacity were less pronounced after treatment with coils. Furthermore, the patients in the study who were treated with coils were one of the first patients ever treated and a best-responder profile for this treatment is not defined yet. Currently, there is more knowledge on the group of patients that will potentially benefit of the treatment with valves than with the treatment with coils.

If we compare our endobronchial valve treatment effects on physical activity with those of pharmacological treatment or pulmonary rehabilitation we must keep in mind that we selected very severe emphysema patients, yet fit enough to undergo endobronchial valve treatment. Three randomized controlled trials investigating a long-acting bronchodilator showed inconsistent results regarding physical activity in patients with mainly moderate COPD. Two studies did not find a significant improvement in physical activity after 3 weeks or 24 weeks of treatment in contrast to one study with 3 week follow up demonstrating that the number of steps increased by 722 steps per day compared to a placebo group.[15,16,17] The results of the effect of pulmonary rehabilitation on physical activity is inconsistent and a review concluded that exercise training (not only rehabilitation) has a small but significant effect on physical activity.[18,19]

Our results showed that physical activity significantly improved after endobronchial valve treatment in the short term up to 6 months after treatment and it would be interesting to also investigate the effects on the longer term. To maintain the effects in the long term, or even further improve them, it could be useful to provide a physical activity enhancement program after the endobronchial valve treatment, for example by following a pulmonary rehabilitation program. Furthermore, physical activity counselling programs focusing on physical activity in daily life showed promising results[20,21] and these programs could also be useful to sustain the effects in the long term.

Increased physical activity was significantly associated with improvements in lung function, exercise capacity and quality of life in patients who received standard medical care or endobronchial valve treatment. This indicates the beneficial effect of the endobronchial valve treatment in addition to standard medical care. However, in the total group receiving

endobronchial valve treatment (including crossover patients) we found no significant associations. Therefore, a larger decrease in hyperinflation is not proportionally associated with a larger improvement in physical activity. Probably other factors play a role as well in the size of the improvement in physical activity after the endobronchial valve treatment. These factors could be psychological factors such as motivation or self-efficacy and/or chronic deconditioning, atrophic muscles or the patient's history of physical activity. A physical activity enhancement program after the endobronchial valve treatment could target these factors as well to increase the physical activity level even more.

We found that sitting time decreased by 11 minutes per day and the EBV group did not significantly differed in the change in sitting time compared to the control group. Sitting time has been associated with an increased risk of mortality, even independent of leisure time physical activity.[22] Furthermore, sedentary time has shown to be an independent risk factor for several health outcomes like cardiovascular risk factors, independently of physical activity.[23] Breaking-up sitting time could be beneficial, as it was shown to be beneficially associated with metabolic risk variables and physical function.[24,25,26] Therefore, it could be important to also pay attention to break-up sitting time besides enhancing physical activity after the endobronchial valve treatment.

A limitation of our study was the relative small sample size and the high number of patients who were lost to follow up. However, we did have a control group which strengthens our findings. A large trial, ideally sham-controlled, would be useful to confirm our results. Furthermore, we only measured physical activity 6 months after the treatment and consequently physical activity was measured during two different seasons, which could strongly influence physical activity. On the other hand, both EBV and control group patients were measured throughout the year. Ideally, physical activity should be measured multiple times throughout 1 year including all seasons.

The primary outcomes of most of the randomized controlled trials investigating a lung volume reduction treatment modality in patients with severe COPD are pulmonary function or exercise capacity (e.g. NETT[27], VENT[28], RENEW [NCT01608490] and LIBERATE [NCT01796392]). Such outcome variables are important to understand and prove the mechanistic benefits of lung volume reduction treatment, but ultimately we need patient-centered outcomes to show that the treatment is also beneficial in the perception of the patient. In this perception the RESET trial demonstrated that quality of life improved after the coil treatment.[29] Another important patient-centered outcome would be physical activity which has been shown to be associated with decreased dyspnea severity, improved muscle function and improved quality of life in patients with COPD.[30,31] Furthermore, physical activity is an important prerequisite for an independent lifestyle and social participation. Therefore, we put forward that physical activity should be considered as an important clinical outcome variable in clinical trials investigating treatments for severe COPD.

CONCLUSION

We found that daily physical activity significantly improved 6 months after bronchoscopic lung volume reduction treatment using one-way endobronchial valves. This improvement was without any specific encouragement on physical activity. Therefore, it would be very interesting to investigate the potential additional effect when combining the endobronchial valve treatment with a physical activity counselling program or pulmonary rehabilitation program.

References

1. Klooster K, ten Hacken NH, Hartman JE, et al. Endobronchial Valves for Emphysema without Interlobar Collateral Ventilation. N Engl J Med 2015; 373: 2325-2335.

2. Garcia-Rio F, Lores V, Mediano O, et al. Daily physical activity in patients with chronic obstructive pulmonary disease is mainly associated with dynamic hyperinflation. Am J Respir Crit Care Med 2009; 180: 506-512.

3. Hartman JE, Boezen HM, de Greef MH, Ten Hacken NH. Physical and psychosocial factors associated with physical activity in patients with chronic obstructive pulmonary disease. Arch Phys Med Rehabil 2013; 94: 2396-2402.e7.

4. Hartman JE, Boezen HM, Heintzbergen S, et al. Daily physical activity after bronchoscopic lung volume reduction: a pilot study. Eur Respir J 2012; 40: 1566-1567.

5. Van Remoortel H, Raste Y, Louvaris Z, et al. on behalf of PROactive consortium. Validity of Six Activity Monitors in Chronic Obstructive Pulmonary Disease: A Comparison with Indirect Calorimetry. PLoS One 2012; 7: e39198.

6. Rabinovich RA, Louvaris Z, Raste Y, et al., PROactive Consortium. Validity of physical activity monitors during daily life in patients with COPD. Eur Respir J 2013; 42: 1205-1215.

7. Miller MR, Hankinson J, Brusasco V, et al., ATS/ERS Task Force. Standardisation of spirometry. Eur Respir J 2005; 26: 319-338.

8. Wanger J, Clausen JL, Coates A, et al. Standardisation of the measurement of lung volumes. Eur Respir J 2005; 26: 511-522.

9. Macintyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J 2005; 26: 720-735.

10. Brooks D, Solway S, Gibbons WJ. ATS statement on six-minute walk test. Am J Respir Crit Care Med 2003; 167: 1287.

11. Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. Respir Med 1991; 85 Suppl B: 25-31; discussion 33-7.

12. Bestall JC, Paul EA, Garrod R, et al. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax 1999; 54: 581-586.

13. Trost SG, McIver KL, Pate RR. Conducting accelerometer-based activity assessments in field-based research. Med Sci Sports Exerc 2005; 37: S531-43.

14. Watz H, Waschki B, Meyer T, Magnussen H. Physical activity in patients with COPD. Eur Respir J 2009; 33: 262-272.

15. O'Donnell DE, Casaburi R, Vincken W, et al., INABLE 1 study group. Effect of indacaterol on exercise endurance and lung hyperinflation in COPD. Respir Med 2011; 105: 1030-1036.

16. Troosters T, Sciurba FC, Decramer M, et al. Tiotropium in patients with moderate COPD naive to maintenance therapy: a randomized placebo-controlled trial. NPJ Prim Care Respir Med 2014; 24: 14003.

17. Watz H, Krippner F, Kirsten A, et al. Indacaterol improves lung hyperinflation and physical activity in patients with moderate chronic obstructive pulmonary disease--a randomized, multicenter, double-blind, placebo-controlled study. BMC Pulm Med 2014; 14: 158-2466-14-158.

18. Watz H, Pitta F, Rochester CL, et al. An official European Respiratory Society statement on physical activity in COPD. Eur Respir J 2014; 44: 1521-1537.

19. Cindy Ng LW, Mackney J, Jenkins S, Hill K. Does exercise training change physical activity in people with COPD? A systematic review and meta-analysis. Chron Respir Dis 2012; 9: 17-26.

20. Altenburg WA, Ten Hacken NH, Bossenbroek L, et al. Short- and long-term effects of a physical activity counselling programme in COPD: A randomized controlled trial. Respir Med 2015; 109: 112-121.

21. Mendoza L, Horta P, Espinoza J, et al. Pedometers to enhance physical activity in COPD: a randomized controlled trial. Eur Respir J 2015; 45: 347-354.

22. Katzmarzyk PT, Church TS, Craig CL, Bouchard C. Sitting time and mortality from all causes, cardiovascular disease, and cancer. Med Sci Sports Exerc 2009; 41: 998-1005.

23. Dunstan DW, Howard B, Healy GN, Owen N. Too much sitting-a health hazard. Diabetes Res Clin Pract 2012; 97: 368-376.

24. Owen N. Ambulatory monitoring and sedentary behaviour: a population-health perspective. Physiol Meas 2012; 33: 1801-1810.

25. Healy GN, Dunstan DW, Salmon J, et al. Breaks in sedentary time: beneficial associations with metabolic risk. Diabetes Care 2008; 31: 661-666.

26. Sardinha LB, Santos DA, Silva AM, et al. Breaking-up Sedentary Time Is Associated With Physical Function in Older Adults. J Gerontol A Biol Sci Med Sci 2015; 70: 119-124.

27. Fishman A, Martinez F, Naunheim K, et al., National Emphysema Treatment Trial Research Group. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. N Engl J Med 2003; 348: 2059-2073.

28. Sciurba FC, Ernst A, Herth FJ, et al, VENT Study Research Group. A randomized study of endobronchial valves for advanced emphysema. N Engl J Med 2010; 363: 1233-1244.

29. Zoumot Z, Kemp SV, Singh S, et al. Endobronchial Coils for Severe Emphysema Are Effective Up to 12 Months following Treatment: Medium Term and Cross-Over Results from a Randomized Controlled Trial. PLoS One 2015; 10: e0122656.

30. Pedersen BK, Saltin B. Evidence for prescribing exercise as therapy in chronic disease. Scand J Med Sci Sports 2006; 16 Suppl 1: 3-63.

31. Esteban C, Quintana JM, Aburto M, et al. Impact of changes in physical activity on health-related quality of life among patients with COPD. Eur Respir J 2010; 36: 292-300.