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Effect of Bronchoscopic Lung Volume Reduction in Advanced Emphysema on Energy Balance Regulation

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Keywords

Emphysema · Lung volume reduction · Energy metabolism

Abstract

Background: Hypermetabolism and muscle wasting frequently occur in patients with severe emphysema. Improving respiratory mechanics by bronchoscopic lung volume reduction (BLVR) might contribute to muscle maintenance by decreasing energy requirements and alleviating eating-related dyspnoea. ***Objective:*** The goal was to assess the impact of BLVR on energy balance regulation. ***Design:*** Twenty emphysematous subjects participated in a controlled clinical experiment before and 6 months after BLVR. Energy requirements were assessed: basal metabolic rate (BMR) by ventilated hood, total daily energy expenditure (TDEE) by doubly labelled water, whole body fat-free mass (FFM) by deuterium dilution, and physical activity by accelerometry. Oxygen saturation, breathing rate, and heart rate were monitored before, during, and after a standardized meal via pulse oximetry and dyspnoea was rated. ***Results:*** Sixteen patients completed follow-up, and among those, 10 patients exceeded the minimal clinically important difference of residual volume (RV) reduction. RV was reduced with median (range) 1,285 mL (−2,430, −540). Before BLVR, 90% of patients was FFM-depleted despite a normal BMI (24.3 ± 4.3 kg/m^2). BMR was elevated by 130%. TDEE/BMR was 1.4 ± 0.2 despite a very low median (range) daily step count of 2,188 (739, 7,110). Following BLVR, the components of energy metabolism did not change significantly after intervention compared to before intervention, but BLVR treatment decreased meal-related dyspnoea (4.1 vs. 1.7, $p = 0.019$). ***Conclusions:*** Impaired respiratory mechanics in hyperinflated emphysematous patients did not explain hypermetabolism. ***Clinical Trial Registry Number:*** NCT02500004 at www.clinicaltrial.gov.

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Introduction

Only very recently, a new chronic obstructive pulmonary disease (COPD) phenotype titled "multi-organ loss of tissue" has been proposed. This phenotype includes those with accelerated emphysema progression and enhanced tissue loss in other extrapulmonary compartments, including muscle and adipose tissue. Disturbed tissue maintenance is associated with worse clinical outcomes [1] and might be the result of changes in whole body energy expenditure.

Whole-body energy expenditure can be distinguished into basal metabolic rate (BMR), diet-induced thermogenesis, and physical activity-induced energy expenditure. BMR is primarily determined by fat-free mass (FFM) and comprises the largest part of total daily energy expenditure (TDEE) [2]. Diet-induced thermogenesis is ±10% of TDEE [3], and physical activity-induced energy expenditure largely depends on physical activity level [4]. Whole-body energy expenditure can only be measured over a prolonged period in daily life using doubly labelled water [5]. This stable isotope methodology is very expensive and requires analytical technology that is available in a limited number of centres worldwide.

In COPD, an increased BMR relative to predicted values has repeatedly been demonstrated [6], which is more aggravated in weight-losing patients [6] and in those with emphysema [7]. Although hypermetabolic at rest, COPD patients do not exhibit increased diet-induced thermogenesis [8]. Besides the proposed triggers for hypermetabolism including activation of brown adipose tissue, inflammation, and increased whole body protein turnover, impaired lung mechanics might also result in hypermetabolism [9]. Emphysema is hallmarked by a reduction in lung elastic recoil and progressive hyperinflation, resulting in elevated airway resistance and contributing to impaired lung mechanics [10]. This results in an increased workload of breathing (mL oxygen cost per litre ventilation) [11]. The increased breathing workload has shown to be more pronounced in patients with low body weight and correlated with the degree of hyperinflation [12].

Pharmacological interventions may alleviate dyspnoea, reduce exercise limitation, and improve quality of life in COPD by decreasing airway resistance and reducing hyperinflation. However, response is limited in patients with predominant emphysema [13]. In selected severe emphysematous patients, bronchoscopic lung volume reduction (BLVR) is an additional treatment option that results in marked benefits in terms of pulmonary function, dyspnoea, exercise capacity, and also physical activity [14, 15]. Furthermore, in a recent post hoc analysis of the STELVIO trial [15], we illustrated a significant increase in body weight, skeletal muscle, and fat tissue, suggesting a positive effect on energy balance regulation [16].

BLVR is a unique model to test the influence of lung mechanics on energy balance regulation, as it diminishes thoracic hyperinflation, reduces breathing frequency, and reduces mechanical constraints on lung volume expansion, thereby improving ventilatory mechanics [17]. Efficacy of this treatment highly depends on advanced patient selection to identify responders to the treatment and thereby creating a homogeneous study population.

We hypothesize that a decline in breathing workload following BLVR would decrease energy expenditure, which might positively influence components and determinants of energy balance. Second, BLVR may also improve dietary intake by alleviating eating associated dyspnoea and meal-related oxygen desaturation [18].

Methods

Participants

Twenty patients with advanced emphysema, an identified target lobe with confirmed absence of collateral ventilation by the Chartis measurement, who underwent BLVR treatment using 1-way endobronchial valves were included in this study. Patients were recruited from the Maastricht University Medical Centre (MUMC+) and University Medical Centre Groningen (UMCG) in the Netherlands from September 2016 until April 2017. The Ethics Committee of Maastricht University Medical Centre approved the study protocol, and all participants provided written informed consent. Procedures were conducted according to the principles of the Declaration of Helsinki. The trial was registered at ClinicalTrial.gov (NCT02500004).

Study Design

The study design is shown in Figure 1. Prior to BLVR treatment, patients underwent a 2-week assessment period.

At day 0, patients were visited at home and received a dose of doubly labelled water. They were also instructed to collect urine samples for assessment of TDEE and to wear an accelerometer for registration of physical activity. Furthermore, patients were asked to record their dietary intake in order to assess if they were in a state of stable energy balance. On day 15, fasted-state urine and blood samples were collected; weight, height, and BMR were assessed; and a meal test was performed (vide infra). This 2-week assessment period was repeated 6 months after BLVR treatment.

Body Composition

Body height was determined to the nearest 0.5 cm while the subjects were standing barefoot. Weight was assessed with a beam scale to the nearest 0.1 kg while the subjects were standing barefoot and in light clothing. FFM was calculated from total body water assessment using the deuterium dilution technique, assuming a hydration fraction of FFM of 73%.

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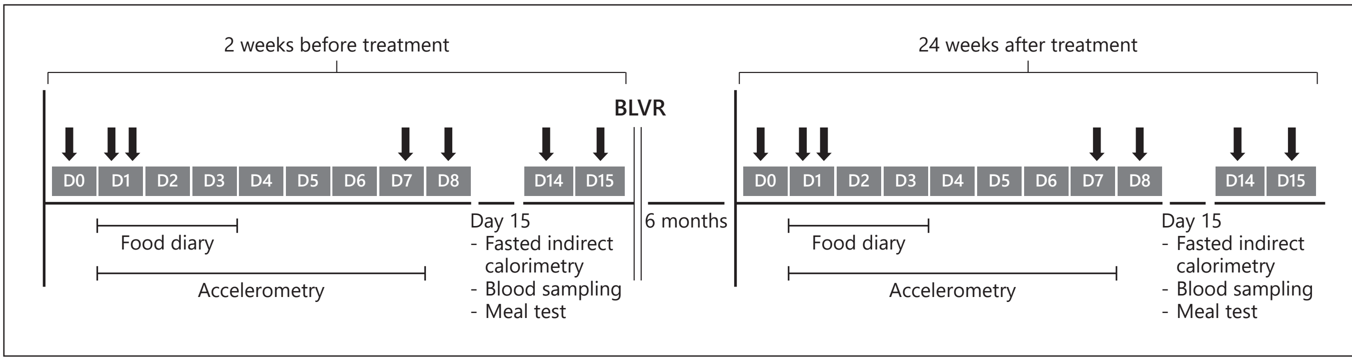


Fig. 1. Study design in days. Black arrows indicate urine sampling.

Resting Metabolic Rate

BMR was measured by indirect calorimetry using a ventilated hood (EZCAL; Maastricht Instruments, Maastricht, the Netherlands and COSMED QUARK; TulipMed B.V., The Netherlands). Patients received their maintenance inhalation according to their normal habits. The time interval between medication use and start of indirect calorimetry was documented. During the second 2-week assessment period 6 months following BLVR treatment, the same time interval between medication use and start of indirect calorimetry was employed. Patients were in a fasting state for at least 10 h and had a period of 30-min bed rest prior to the measurement during which subjects were lying on bed in supine position. After stabilization, BMR was recorded during a period of 30 min. BMR was calculated from oxygen consumption (VO_2) and carbon dioxide (VCO_2) production using the abbreviated Weir formula [19]. BMR was also predicted using the equation from Slinde et al. [20], which was especially designed for COPD patients.

Total Daily Energy Expenditure

TDEE was determined by the doubly labelled water technique over two 2-week periods (before and after BLVR treatment) according to the Maastricht protocol [21]. In the evening, prior to dosing, a urine sample was collected for determination of background isotope enrichment. Each patient received a weighted oral dose of water labelled with deuterium and oxygen-18. The given dose was calculated based on the subjects' total body water, which was estimated based on BMI, age, and gender. Subjects received a dose of 2.5 g/L total body water containing 250 ppm deuterium and 2,200 ppm oxygen-18. After overnight equilibration, a second urine sample was collected from the second morning voiding. Additional urine samples were collected in the evening of days 1, 7, and 14 and in the morning of days 8 and 15. TDEE was calculated by the linear regression from the difference between elimination constants of deuterium and oxygen-18.

Physical Activity

Actigraph GTX3 accelerometers (Actigraph, Pensacola, FL, USA) were used to assess the physical activity level. This activity monitor has been validated against activity-related energy expenditure measured by doubly labelled water in patients with different stages of COPD [22]. The triaxial accelerometers were attached to the lower back with an elastic belt and worn for 7 consecutive days. Subjects were instructed to wear the accelerometer during the time they were not asleep, except when showering or bathing. Only days with ≥8 h of wear time were accepted as valid days. Energy expenditure for activities was calculated by (0.9 × TDEE) – BMR, assuming a diet-induced thermogenesis of 10% of TDEE.

Dietary Intake

Food intake was recorded by a food diary for 2 week days and 1 weekend day to estimate baseline energy balance.

Meal Test

On the measurement day at the hospital, subjects received a standardized breakfast with wheat bread, butter, eggs, and milk. This meal contained a total of 502 kcal derived from protein (24%), carbohydrate (28%), and fat (48%). Oxygen saturation, breathing rate, and heart rate were monitored before, during, and after the breakfast via pulse oximetry. Before and immediately after the meal, dyspnoea was rated using the Borg Dyspnoea Scale.

Systemic Inflammatory Status

High-sensitive C-reactive protein (hsCRP) was assessed from frozen stored plasma collected from a venepuncture after overnight fasting.

Statistics

Descriptive statistics of demographic and clinical variables were obtained. Means (±SD) were provided for continuous normally distributed variables, medians (interquartile range) for continuous not normally distributed variables, and percentages were shown for categorical variables. Baseline and 6-month follow-up measurements were compared with a paired-sample t test or Wilcoxon signed-rank test. All analyses were performed using SPSS statistical software (SPSS Statistics for Windows, version 24.0; IBM, Armonk, NY, USA). Results with 2-sided p values (<0.05) were considered statistically significant.

Results

Patient Characteristics

Twenty patients (7 men, 13 women) with severe emphysema (n = 10 MUMC+ and n = 10 UMCG) were enrolled in this study, and 16 patients completed the follow-

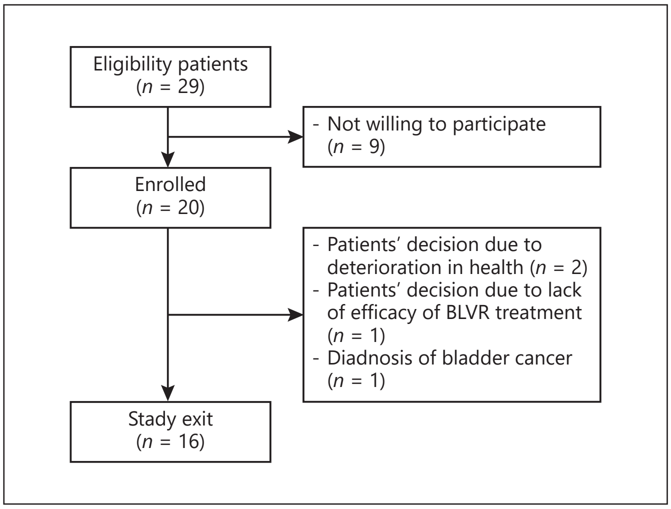


Fig. 2. Study flowchart.

Table 1. Baseline characteristics ($N = 20$)

General	
Male/Female, *n*	7/13
Age, years	63±7
Pack, years	42±25
Lung function	
FEV_1, % predicted	23.3±6.6
FVC, % predicted	76.2±15.9
FEV_1/FVC	28.5±6.3
RV, % predicted	238.3±38.2
TLC, % predicted	136.6±17.9
RV/TLC	64.7±9.4
Body composition	
Weight, kg	70.3±16.3
BMI, kg/m^2	24.1±4.4
FFM, kg	38.2 (32.1–57.4)
FFMI, kg/m^2	
Male	15.1 (14.7–16.2)
Female	13.5 (12.1–18.1)

Data are represented as mean ± SD or median (minimum-maximum). FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity; FFM, fat-free mass; FFMI, fat-free mass index.

up. Reasons for drop out were patients' decision due to deterioration in health ($n = 2$), patients' decision due to lack of efficacy of BLVR treatment ($n = 1$), and diagnosis of bladder cancer ($n = 1$). In 4 of the 16 patients who completed follow-up, endobronchial valves were removed due to granulation tissue around endobronchial valves ($n = 2$), torsion bronchus ($n = 1$), and recurrent pneumothorax ($n = 1$) (Fig. 2).

Baseline characteristics are depicted in Table 1. The study population represented a COPD population with normal BMI (24.1 ± 4.4 kg/m^2) and low FFM (FFM index: males 15.1 kg/m^2 [14.7, 16.2], females 13.5 kg/m^2 [12.1, 18.1]). The prevalence of depletion of FFM, defined as FFM index ≤17 kg/m^2 for males or ≤15 kg/m^2 for females [23], was 90%.

Baseline Assessment

At baseline, the mean BMR was 1,537 ± 259 kcal/day, which corresponded to 130% of predicted, indicating pronounced hypermetabolism. The average TDEE over 2 weeks was 2,133 ± 294 kcal/day. The average daily TDEE of week 1 was not statistically significantly different from the average daily TDEE of week 2. Energy expenditure for activities was median (range) 275 kcal/day (138, 827) (11% of TDEE).

Among those who completed follow-up, from all subjects but 2 (due to an accelerometer device defect), 6.5 ± 1.1 valid accelerometry days were available with a mean of 13 ± 1 h of wear time per day. Median (range) steps per day was 2,188 (739, 7,110). Patients spent a significant part of the day in sedentary state (79.7% of the wear time [56.5, 89.6]) (Table 2).

Systemic inflammation measured by hsCRP was 3.0 ± 2.7 mg/L. BMR or TDEE was not associated with hsCRP or residual volume (RV) (% of predicted) (data not shown). Reported dietary intake comprised 2,065 ± 507 kcal/24 h, which equalled measured TDEE. Patients experienced more dyspnoea after eating (4.1 ± 1.8 after meal vs. 2.1 ± 2.1 before meal, $p = 0.013$). No significant change was shown in oxygen saturation, respiration rate, and heart beat rate during the course of the meal (Fig. 3).

Response after BLVR

Not all patients benefited from the BLVR treatment, in terms of hyperinflation reduction. We therefore took a closer look at the 10 patients who responded beyond the MCID for RV reduction of >430 mL [24]. At 6-month follow-up, patients significantly improved in RV and forced expiratory volume in 1 s, with 1,285 mL (−2,430, −540) and 190 mL (10, 390), respectively.

BMR did not significantly change over time (1,537 ± 259 kcal/day vs. 1,549 ± 231 kcal/day, $p = 0.778$), and patients remained hypermetabolic (BMR was 130% of predicted). No changes in TDEE were observed (2,133 ± 294 kcal/day vs. 2,192 ± 480 kcal/day, $p = 0.576$), in accordance with an unaltered physical activity expressed by mean number of daily steps. Although 6-min walk distance increased significantly, the mean step

Table 2. Clinical variables and components of energy balance at baseline and 6 months after BLVR treatment (n = 10)

	Baseline	After BLVR	p value
Lung function and symptom burden			
FEV_1, % of predicted value	27.5±6.9	34.9±8.3	**0.003**
FVC, % of predicted value	74.4±15.0	95.1±17.1	**<0.001**
FEV_1/FVC	30.5±7.2	29.5±5.6	0.591
RV, % of predicted value	236.2±37.6	181.3±27.5	**<0.001**
TLC, % of predicted value	135.0±20.0	125.1±14.7	**0.007**
RV/TLC	65.8±6.2	51.3±6.1	**<0.001**
COPD assessment test, points	18.6±3.4	14.3±5.8	**0.022**
6MWD, m	378±98	427±84	**0.030**
Body composition			
Weight, kg	71.4±17.4	73.0±18.7	0.096
BMI, kg/m^2	24.3±4.3	24.8±5.0	0.127
FFM, kg	40.4 (32.2–57.4)	41.1 (29.4–60.2)	0.074
FFMI, kg/m^2			
Male	15.5 (14.7–16.2)	16.6 (15.5–18.6)	0.068
Female	13.2 (12.4–17.6)	13.6 (12.1–17.3)	0.600
Energy expenditure			
VCO_2, mL/min	179.5±26.1	180.5±28.6	0.854
VO_2, mL/min	224.7±40.0	224.0±3.1	0.903
RQ	0.81±0.07	0.81±0.05	0.916
BMR measured, kcal/day	1,537±259	1,549±231	0.778
BMR predicted, kcal/day	1,213±155	1,245±189	0.103
BMR measured/BMR predicted ratio	1.3±0.2	1.2±0.1	0.655
TDEE, kcal/24 h	2,133±294	2,192±480	0.576
TDEE/BMR ratio	1.4±0.2	1.4±0.3	0.934
Energy expenditure for activities, kcal/day	275 (138–827)	397 (18–1,262)	0.694
Energy expenditure for activities/TDEE ratio	0.2±0.1	0.2±0.1	0.995
Physical activity level			
Mean steps/day	2,188 (739–7,110)	2,429 (990–6,983)	0.161
Time spent in sedentary PA, % of wear time	79.7 (56.5–89.6)	79.4 (52.7–84.2)	0.123
Time spent in lifestyle PA, % of wear time	17.6 (10.1–34.2)	18.6 (14.1–37.9)	0.123
Time spent in MVPA, % of wear time	0.0 (0.0–1.1)	0.2 (0.0–1.4)	**0.028**
Inflammation			
hsCRP, mg/L	3.0±2.7	2.5±1.8	0.463

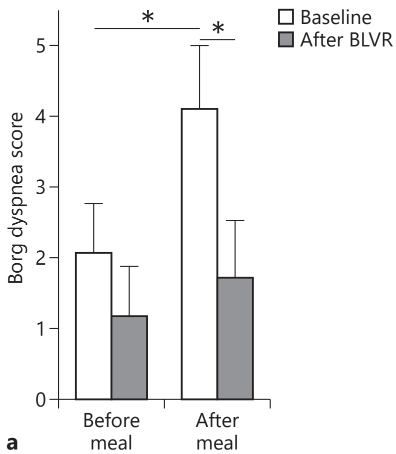
Data are represented as mean ± SD, or median (minimum-maximum). Values in bold are statistically significant. COPD Assessment Test, missing n = 2 FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity; FFM, fat-free mass; FFMI, fat-free mass index; 6MWD, 6-min walk distance; MVPA, moderate-to-vigorous physical activity; PA, physical activity; BMR, basal metabolic rate; TDEE, total daily energy expenditure; hsCRP, high-sensitive C-reactive protein.

count and activity-induced energy expenditure did not change over time. hsCRP also remained unchanged (Table 2).

A significant effect of BLVR treatment on meal-related dyspnoea was observed. Compared to baseline, meal-related dyspnoea after the meal was significantly lower after BLVR treatment (1.7 ± 2.4 vs. 4.1 ± 1.8, p = 0.019). No changes were found in oxygen saturation, respiration rate, or heart rate during the meal (Fig. 3).

Discussion

This is the first study presenting a comprehensive analysis of energy balance in a homogeneous group of patients with severe emphysema and investigating the effect of BLVR. In contrast to our hypothesis, a median reduction of hyperinflation with 25% did not decrease BMR or TDEE adjusted for physical activity level. Eating-related dyspnoea, however, was diminished.



a

		Baseline	After BLVR	p-value
Borg dyspnoea score	Before meal	2.1 ± 2.1	1.3 ± 2.1	0.359
	After meal	4.1 ± 1.8	1.7 ± 2.4	0.019
Oxygen saturation, %	Before meal	93.2 ± 2.4	92.2 ± 3.1	0.193
	During meal	92.5 ± 3.6	91.9 ± 3.3	0.272
	After meal	92.0 ± 3.1	92.4 ± 3.7	0.406
Respiration rate (respirations/min)	Before meal	16.1 ± 3.7	16.5 ± 2.6	0.647
	During meal	16.7 ± 3.7	16.6 ± 3.4	0.850
	After meal	16.0 ± 4.5	17.1 ± 3.2	0.465
Heart rate (beats/min)	Before meal	74.6 ± 8.7	70.1 ± 10.2	0.155
	During meal	82.2 ± 8.4	77.4 ± 10.4	0.167
	After meal	83.1 ± 9.8	77.3 ± 11.3	0.134

b

Fig. 3. Borg Dyspnoea Score (**a**), Borg Dyspnoea Score, oxygen saturation, respiration rate, and heart rate before, during, and after completion of a standardized meal, before, and after bronchoscopic lung volume reduction (BLVR) treatment (n = 10) (**b**). Data are presented as mean values (±standard deviation).

In line with the "multiorgan loss of tissue" phenotype [1], we observed a very high prevalence of FFM depletion indicative for disturbed muscle maintenance. Nearly all patients were FFM-depleted, but this was disproportionate to the FM as the majority of patients fell within a normal BMI range. Before BLVR, BMR was very high, up to 130% of predicted and energy expenditure for physical activities was very low (11%). This implies that in this patient group and at this stage of the disease, fat mass regulation is primarily determined by the balance between energy intake and whole body energy requirements and less or not yet by fat catabolism (i.e., increased lipolysis or brown adipose tissue activation). The normal BMI in this population hides FFM depletion, emphasizing the importance of body composition assessment for estimation of metabolic risk as proposed by the European Respiratory Society Task Force on nutritional assessment and therapy in COPD [25].

No studies to date have investigated the effect of lung volume reduction on TDEE, but a few studies previously reported the effect of lung volume reduction surgery on BMR. Mineo et al. [26] showed a reduction of BMR with 5%, while Takayama et al. [27] observed no change in BMR. The degree of hyperinflation reduction was comparable to our cohort. Nevertheless, one needs to consider that although our patients improved importantly after intervention, they still remain severely hyperinflated with a mean RV of 181% of predicted.

A contributor to BMR is whole body protein turnover, which explained approximately 20% of the between-subject variation of BMR in healthy young individuals [28]. Also in COPD, increased rates of whole body protein turnover have been reported [29, 30], which is associated with BMR [31]. Increased muscle turnover signalling was accompanied with elevated myogenic signalling [32], which was most prominent in patients with FFM depletion. Therefore, persistence of high BMR after BLVR might be the result of energy cost of protein anabolism, supported by increased muscle mass observed previously in chest CT scans [16].

In the absence of catabolic drivers, fat mass is primarily regulated by the balance between energy intake and energy metabolism. In line with others [33, 34], our patients experienced an eating induced increase in dyspnoea. Vermeeren et al. [33] reported the effects of different meals on dyspnoea sensation and found a significantly greater increase in dyspnoea after ingestion of a fat-rich meal than after a carbohydrate-rich meal. Here, we show for the first time that dyspnoea after the same, standardized meal was significantly less following BLVR. In line with 2 other studies, these effects could not be explained by changes in meal-related oxygen saturation [18, 33].

Systemic inflammation has been proposed as putative trigger for hypermetabolism, in particular during acute exacerbations [35, 36]. Indeed, elevated CRP levels have previously been associated with higher BMR in clinically stable COPD [37, 38]. In this study, CRP levels were slightly elevated but did not change after BLVR.

The strength of this prospective well-controlled clinical proof of concept study comes from the well-defined patient cohort and from the use of gold standard methods to assess body composition, BMR, and TDEE. We recognize that the study power was based on detection of changes in energy metabolism in relation to changes in lung function but not on changes in body composition. The technique of pulse oximetry has the advantage of providing a continuous and non-invasive measurement of oxygen saturation. However, this technique is limited by a poorer accuracy of 1–3% when compared to arterial blood sampling [39]. To conclude, the present work showed that impaired respiratory mechanics in hyperinflated emphysematous patients did not explain hypermetabolism.

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Statement of Ethics

The Ethics Committee of Maastricht University Medical Centre approved the study protocol, and all participants provided written informed consent before initiation of study measurements. Procedures were conducted according to the principles of the Declaration of Helsinki. The trial was registered at ClinicalTrial.gov (NCT02500004).

Conflict of Interest Statement

K.J.C.S., L.E.G.W.V., G.P., and A.M.W.J.S. had nothing to disclose. K.K. reports grants, personal fees, non-financial support, and other from PneumRx/BTG (Mountain View, CA, USA), and grants, personal fees, non-financial support, and other from PulmonX (Redwood City, CA, USA), outside the submitted work. A.-M.C.D. reports personal fees from Roche, Boehringer Ingelheim, Eli Lily, Novartis, Takeda, and BMS, outside the submitted work. D.J.S. reports grants, personal fees, non-financial support ,and other from PulmonX Inc. (Redwood City, CA, USA), outside the submitted work.

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Author Contributions

A.M.W.J.S., L.E.G.W.V., and D.J.S. designed research; K.J.C.S. and K.K. conducted research; G.P., K.J.C.S., K.K., and A.M.W.J.S. analysed data; K.J.C.S. performed statistical analysis; K.J.C.S. and A.M.W.J.S. wrote the paper with input from K.K., L.E.G.W.V., G.P., A.-M.C.D., and D.J.S.; and all authors read and approved the final manuscript. K.J.C.S. had primary responsibility for the final content.

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