ONLINE SUPPLEMENT

Bronchoscopic lung volume reduction treatment using endobronchial valves for emphysema: emerging questions

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PROTOCOL

SoLVE study

A prospective randomized controlled trial on the **S**ystemic effects of bronchoscopic **L**ung **V**olume reduction in patients with severe **E**mphysema.

(29-05-2018)

PROTOCOL TITLE: A prospective randomized controlled trial on the **S**ystemic effects of bronchoscopic **L**ung **V**olume reduction in patients with severe **E**mphysema ’

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Pharmacy	*Not applicable*

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	Adverse Event
CV	Collateral Ventilation
DSMB	Data Safety Monitoring Board
GCP	Good Clinical Practice
METC	Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)
(S)AE	(Serious) Adverse Event
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen.

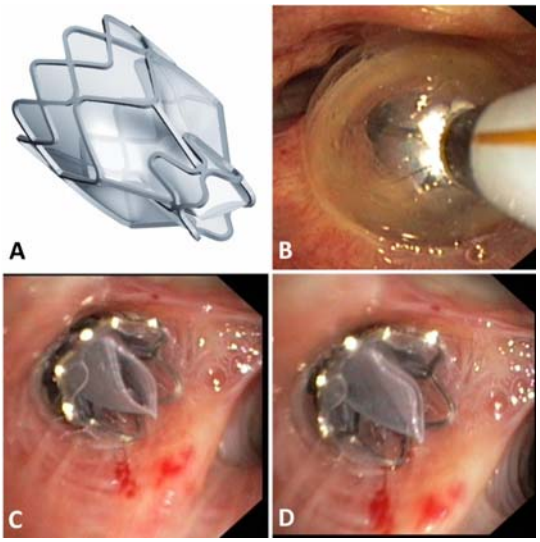
SUMMARY

Rationale: The published clinical trials investigating the bronchoscopic lung volume reduction, showing important patient-related improvements in efficacy, led to the acknowledgement of the treatment in the GOLD-COPD2017 guidelines. Interaction with pulmonary rehabilitation, impact on patient-reported outcomes, physical activity, and extrapulmonary consequences are all topics to gain more insight in. This importantly, to further develop and optimize this innovative and personalized therapy.
Objective: To study in detail the impact and optimal timing of pulmonary rehabilitation (PR) on exercise physiology and patient-reported outcomes and the impact of the bronchoscopic lung volume reduction treatment using endobronchial valves (EBV) on cardiopulmonary function, metabolism and changes in body composition.
Study design: This study is a randomized controlled trial with 3 study-arms. Group 1 will first follow a PR program and afterwards undergo the EBV treatment. Group 2 will first undergo the EBV treatment and approximately 8 weeks later will follow a PR program. Group 3 will only undergo the EBV treatment (and can choose to follow a PR program after completing the 6 month FU visit).
Study population: The study population exists of patients with severe emphysema who undergo a bronchoscopic lung volume reduction treatment using one-way valves.
Intervention: Most patients will undergo a bronchoscopic lung volume reduction treatment using endobronchial valves and a pulmonary rehabilitation program. One group of patient will under a bronchoscopic lung volume reduction treatment using endobronchial valves and can choose whether they also want to follow a pulmonary rehabilitation program afterwards.
Main study parameters: The main study parameter is the difference in change in endurance time measured by an endurance cycle test between the EBV treatment group and the bronchoscopic lung volume reduction + rehabilitation group (EBV+PR) between baseline and 6 month follow up.
Nature and extent of the burden and risks associated with participation, benefit and group relatedness: This study has no major risks for the participating patients. The patients will be exposed to additional exercise capacity and physical activity measurements, 2 additional questionnaires, a CT scan of the quadriceps muscle, a DEXA scan and peripheral blood collection. Furthermore, a subgroup of patients will be exposed to a cardiac MRI and patients can choose to undergo muscle and/or fat biopsies. Patient can directly benefit from the EBV treatment and the pulmonary rehabilitation program. Indirect benefit might be achieved, because, at a group level we will learn more about this novel treatment for our severe emphysema patients and will be able to further optimize this treatment.

1. INTRODUCTION AND RATIONALE

1.1 EBV treatment

Patients with severe COPD suffer from dyspnea with great impact on quality of life. COPD is an incurable disease. Holistic treatment includes smoking cessation, optimal nutrition, vaccination, pulmonary rehabilitation and pharmacological therapies. However, treatment response is limited, with lung volume reduction surgery (LVRS) or lung transplantation remaining optional for few patients (Vogelmeier, 2017). In COPD patients characterized by emphysema, innovative and minor invasive bronchoscopic therapeutic strategies have been developed (Shah, 2016).



One of the emerging therapies is bronchoscopic lung volume reduction using one-way endobronchial valves (EBV), designed to unilaterally occlude the most diseased lobe of the lung in patients with absence of interlobar collateral ventilation, thereby reducing hyperinflation *(See figure 1)* (Shah, 2016, Herth, 2016, Herth, 2013, Klooster, 2015).

Figure 1A-D. A) *One-way endobronchial valve* ***B)*** *Chartis catheter to measure collateral ventilation,* ***C)*** *EBV appearance on expiration allowing lobar air to exit,* ***D)*** *EBV appearance on inspiration, closing to avoid air from entering the most diseased lobe.*

Recently, we reported significant improvements in lung function (FEV_1 +18%), exercise capacity (6MWD +74m) and quality of life (SGRQ -15points improvement) after EBV treatment (Klooster, 2015). Without any further intervention, these patients also improved in physical activity as measured by a mean increase of 1340 steps/day (+47%) (Hartman, 2016). This indicates that EBV treatment leads to real life improvements, with potentially important systemic changes at metabolic, inflammatory and physiologic levels. After the publication of this landmark study, 2 larger randomized controlled trials in both homogeneous and heterogeneous emphysema confirmed our initial findings (Kemp, 2017, Valipour, 2016).

These scientific achievements resulted for the first time in the acknowledgement of EBV treatment in the GOLD-COPD2017 guidelines (Vogelmeier,2017), with the comment that "additional data are needed to define the optimal patient population to receive the specific bronchoscopic lung volume reduction technique and to compare long term durability of improvements in functional or physiological performance".

Fully in line with the above, all clinical trials showed the challenges of this treatment as well as striking outcomes in a patient population deemed to have no therapeutic options anymore. Interaction with pulmonary rehabilitation, impact on quality of life, physical activity, and extrapulmonary consequences are all topics to gain more insight in (Vogelmeier ,2017). This importantly, to further develop and optimize this innovative and personalized therapy, and to gain knowledge on the impact of modifying the severe emphysema disease state for the individual patient. Therefore, the overall aim is:

To study in detail the impact and optimal timing of pulmonary rehabilitation on exercise physiology and patient-reported outcomes and the impact of EBV treatment on cardiopulmonary function, metabolism and body composition.

The overall aim can be divided into 4 subthemes: pulmonary rehabilitation, patient-reported outcomes, cardiopulmonary function and metabolism and change in body composition.

1.2 Pulmonary rehabilitation

As stated in the GOLD guidelines, pulmonary rehabilitation should be considered part of integrated patient management (Vogelmeier,2017). Therefore, most clinical trials investigating the EBV treated included only patients who followed regular maintenance physical therapy. The question arises whether patients would benefit more from the combination of EBV therapy AND pulmonary rehabilitation and what would be the best timing of the pulmonary rehabilitation program, before or after the EBV treatment.

Volume reduction in emphysema serves to enhance the relationship between effort and ventilatory output by 1) reducing the elastic load and increasing the functional strength of the inspiratory muscles which, and 2) increasing the extent to which these fibers can shorten. To the extent that exertional breathlessness arises when there is marked restriction of lung and thoracic motion despite inspiratory efforts that approach maximal pressure generating capacity, volume reduction should improve thoracic mobility and reduce effort requirements for any given breath which should, in turn, translate into diminished breathlessness. The neurophysiologic corollary of this is that less neural activation is required for a given ventilatory output (ie, enhanced neuromechanical coupling). The impairment of exercise tolerance occurs as a result of both ventilatory limitation, and deconditioning and distinct abnormalities in the muscles of ambulation. Pulmonary rehabilitation (PR) has repeatedly and consistently been shown to enhance exercise tolerance as well as improve dyspnea without necessarily improving the mechanics of the respiratory system. As EBV treatment improves ventilatory mechanics as discussed above, it seems likely, that these improvements would permit an enhanced ability to train and augment the exercise tolerance benefits observed with PR (see model in figure 2).

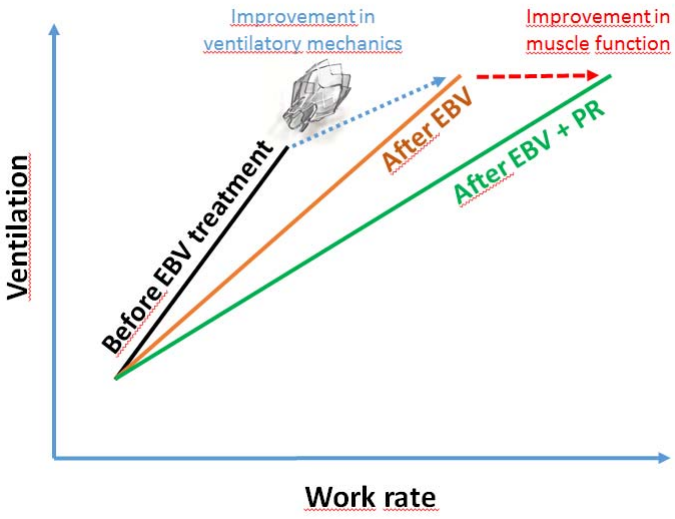


Figure 2*. Hypothetical model of work rate in function of ventilation. Before bronchoscopic lung volume reduction ventilation is restricted, which is improved after one-way endobronchial valve treatment. After additional pulmonary rehabilitation (PR), ventilation for a given exercise (iso-exercise) is further improved.*

Indeed, reductions in hyperinflation permit tidal volume expansion during exertion such that the ventilatory limitation to the performance of work is reduced (O'Donnell ,1993). Patients

may be able to exercise longer or with a higher intensity, thereby inducing an improved physiologic training effect on the muscles of ambulation. This may yield superior gains in exercise tolerance. Patients may engage in daily activities for longer periods of time, which may also contribute to benefits observed from formal exercise training. Furthermore, benefits gained may have a longer-lasting effect due to the higher exercise tolerance attained. Casabury et al showed in a placebo controlled study that receiving tiotropium showed significantly longer exercise endurance time at the conclusion of PR compared to patients in the control group (Casaburi, 2005). Tiotropium has been shown to improve hyperinflation over 24h and improve continuous work rate endurance on cycle ergometry (O'Donnell, 2004).
We aim to investigate exercise physiology before and after EBV treatment and after a consequent pulmonary rehabilitation program in a RCT design (see methods) and to explore the timing of pulmonary rehabilitation in EBV treated patients (figure 3).

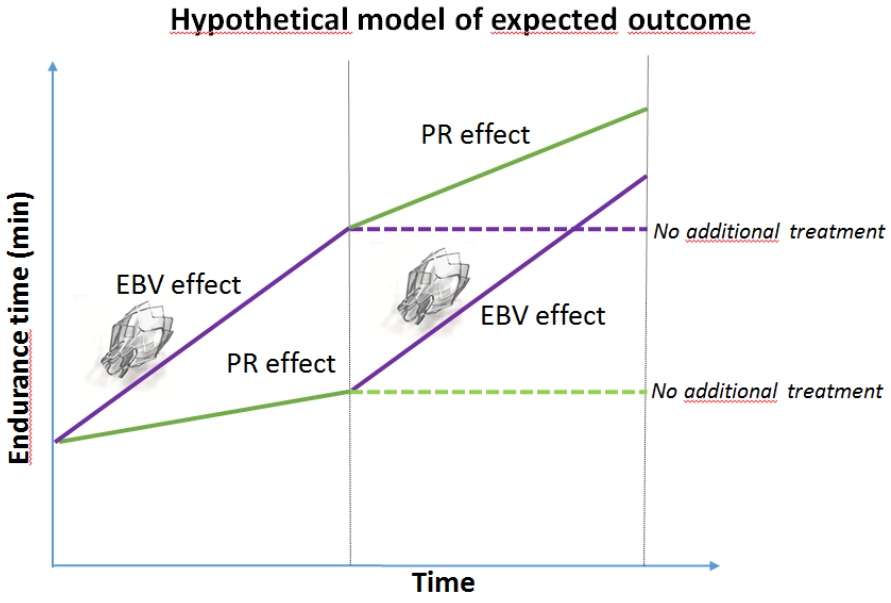


Figure 3. *Hypothetical model of expected outcome for the different study arms and study phases of the proposed RCT. Patients treated with EBV (purple line) have increased endurance time after treatment compared to the PR group (green line). PR after EBV treatment leads to an increased endurance time compared to PR before EBV treatment.*

1.3 Patient-reported outcomes

Although dyspnea is a somatic signal of danger, it might be misinterpreted as life threatening (ie, the feeling of not able to breath), leading to anxiety and panic attacks. This in turn might lead to heightened physiological arousal, followed by increased symptoms of anxiety. This vicious circle of dyspnea and anxiety is common among patients with COPD (VanFleteren, 2016). Static and dynamic lung hyperinflation have major implications for dyspnea and exercise limitation, quality of life and survival and are more closely associated with symptoms and exercise performance than spirometry (O'Donnel, 1993; Lange, 2014). Hence, symptoms of anxiety and depression are likely to respond to EBV treatment. Indeed, high dyspnea sensation is highly related to anxiety and even panic attacks, which in turn might result in uncontrolled breathing patterns, increasing dynamic hyperinflation, and increased dyspnea. This spiral might even result in hospital admission (VanFleteren, 2016). Fatigue is an important and barely investigated problem in patients with COPD and is thought to be multifactorial, related to exercise intolerance, physical inactivity, nocturnal dyspnea, symptoms of anxiety and depression, pharmacological therapy, etc. As patients improve in quality of life, exercise capacity and physical activity, we hypothesize that patients might improve in fatigue. This study also provides additional information of the etiology of fatigue

in COPD, as it might serve as a proof of concept of the relation of COPD severity and dyspnea severity with fatigue.
Therefore we aim to study changes in symptoms of anxiety, depression and fatigue, in patients undergoing EBV and EBV+PR. Furthermore, to study the relationship between changes in these symptoms and physiological changes like lung function and exercise capacity.

1.4 Cardiopulmonary function

Until now, no studies have investigated the cardiopulmonary function before and after EBV treatment. In cross-sectional studies, increased levels of static lung hyperinflation and emphysema are associated with reduced cardiac chamber size and function (Barr, 2010). Using a thermodilution technique, significant changes in indexes of right ventricular function 6 months after lung volume reduction surgery have been observed, consistent with an improved performance of the right ventricle. The significant relationship found between improvement in the exercise response of RVEF and the reduction in the RV/TLC ratio suggested that reduced lung hyperinflation exerts beneficial effects on right ventricular filling and performance (Mineo, 2002). Also pharmacologically induced lung deflation is associated with consistent beneficial effects on cardiac structure, function, and pulmonary vasculature using cardiac MRI (Stone, 2016). Studies investigating cardiac function in COPD have traditionally used echocardiography which is limited due to poor acoustic windowing in hyperinflated lungs, or cardiopulmonary exercise testing which represents surrogates of cardiac function, or thermodilution techniques which are invasive. Cardiac magnetic resonance imaging (MRI) provides unparalleled image quality noninvasively, with excellent accuracy and reproducibility of cardiac structure and function (Hudsmith, 2005). Furthermore, novel imaging techniques allow tracking of myocardial deformation, providing information on intrinsic function (Stone, 2016). Reduced right ventricular size in hyperinflated COPD has been a consistent finding in recent cardiac MRI studies. Right ventricle end-diastolic volume (RVEDV) indexed to body surface area, the suggested primary endpoint for this part of our study, has been shown to be reduced in patients with severe emphysema compared with age, sex, and body size matched control subjects (Jörgensen, 2007). In a prospective, multicenter, cohort study of more than 6,000 participants, involving two subgroups from the Multi-Ethnic Study of atherosclerosis (MESA), a 10% increase in CT-defined emphysema was associated with a reduction in RVEDV (Grau, 2013). RVEDVI is selected as our primary endpoint because the thin-walled RV is considered most sensitive to changes in preload conditions, as also suggested by Stone et al (Stone, 2016) .

Reduced cardiac chamber size in COPD has been attributed to the stiffening of the mediastinum or, alternatively, decreased ventricular preload through vascular remodeling in emphysema or increased intrathoracic pressure caused by gas trapping and airflow obstruction (Stone, 2012). Subclinical changes in right ventricular morphology have recently been shown to affect patient centered outcomes. On a population level, one SD decrement (11ml/m2) in RVEDVI has been associated with a 12% increase in the risk of dyspnea after adjustment for spirometric measurements and CT-defined emphysema (Kaufmann, 2013). Furthermore, increases in cardiac output are associated with improvements in walking intensity across all severities of COPD (Louvaris, 2013). The ability to modify cardiac morphology and function does therefore seem to independently impact on relevant clinical and patient centered outcomes (Vanfleteren, 2014).

Therefore, we aim to study the effect of EBV on the change in RVEDVI, and other pre-specified outcome of cardiac structure and function as measured with cardiac MRI and the relative contribution of improvement in RVEDVI to the improvement in exercise capacity and/or physical activity after EBV.

1.5 Metabolism and change in body composition

The effect of the EBV treatment on metabolism and body composition is not clear. Emphysematous COPD patients suffer frequently from unintended weight loss and muscle wasting adversely affecting quality of life and prognosis (Vanfleteren, 2013). Weight loss and fat loss result from a negative balance between energy requirements and energy intake. It is established that deviations in both sides of the balance are present in emphysematous patients. It is hypothesized that impaired lung mechanics in emphysema negatively influences the energy balance. This hypothesis is indirectly supported by a positive effect of lung volume reduction surgery on resting energy expenditure (REE) and body weight in emphysema (Mineo, 2006, Mineo, 2010). Otherwise, in contrast to expected decreased protein turnover rates during semi-starvation, increased REE is associated with increased rates of protein turnover in severe COPD, related to altered muscle maintenance regulation (Langen, 2013). Furthermore Baarends et al. showed that there is no significant difference in total daily energy expenditure (TEE) assessed by doubly labelled water between clinically stable COPD patients with a normal REE and those with an increased REE. The variation in TEE in patients with clinically stable COPD appears to reflect differences in physical activity induced energy expenditure (Baarends,1997). Furthermore, Improved ventilatory capacity after EBV treatment induces an increase in exercise capacity (figure 2). However, the contribution of changes in body composition to this increase in exercise capacity is unknown. In a post-hoc analysis of the STELVIO trial (Klooster, 2015), we investigated the impact of EBV treatment on body composition in severe emphysema, where we observed changes within the muscle compartment that contributed to increased exercise capacity, independently from the degree of reduction of hyperinflation (data not published). Remarkable EBV treatment induced not only an increase in muscle cross-sectional area but also in intramuscular adipose tissue and both compartments were positively associated with improved exercise performance after EBV treatment. The observed remodeling may enhance exercise performance and daily activities by improving muscle strength, but also by alleviating fatigue. In line with the athlete's paradox, we hypothesize that the observed increase in intramuscular adipose tissue reflects improved muscle mitochondrial metabolism and insulin sensitivity, via an effect of PPARγ coactivator-1 (PGC1) on intramuscular lipid programming (Koves, 2013). Supportive for this hypothesis are two studies by Mineo et al showing that a decrease in REE after lung volume reduction surgery was associated with a conversion from prevalent lipid to prevalent carbohydrate metabolism (Mineo, 2006) and demonstrating a reduction in insulin resistance (Mineo,2008). Improved PGC1 expression induced muscle mitochondrial metabolism may increase physical activity level by decreasing muscle fatigue and positively affecting mood via muscle-brain cross-talk (i.e. kynurenine metabolism) (Agudelo, 2014).

We aim to prospectively study the role of increase in muscle volume in the improvement of exercise capacity, and whether and to what extent it explains the variance in this improvement in exercise capacity in addition to changes in lung mechanics, and cardiac alterations. Furthermore, we will investigate detailed histological and biochemical analysis of

muscle fiber type composition, mitochondrial density, master regulators of muscle oxidative programming, mitochondrial respiration and lipid droplets.
Furtermore, adipose tissue inflammation contributes to systemic inflammation in COPD patients (Borst et al. AJCN 2013, Rutten, 2010). Adipose tissue is an active producer of mediators involved in inflammation, the so-called adipokines of which leptin and adiponectin are examples. The latter potentially have a role in development and/or protection of lung disease/emphysema (Vanfleteren/Slebos Respiration 2017). We aim to prospectively study the influence of EBV treatment with and without PR on systemic and fat inflammatory state.

2. OBJECTIVES

Primary Objective:
To investigate the difference in change in exercise capacity measured by an endurance cycle test between the bronchoscopic lung volume reduction using endobronchial valves (EBV) treatment group and the bronchoscopic lung volume reduction + rehabilitation group (EBV+PR) between baseline and 6 months follow up.

Secondary Objectives:
Pulmonary rehabilitation
- To investigate the difference in change in physical activity, lung function, exercise capacity and peripheral muscle strength between the EBV treatment group and the EBV+PR group between baseline and 8 weeks and 6 months follow up.
- To investigate the difference in change in patient-reported outcomes between the EBV treatment group and the EBV+PR group between baseline and 8 weeks and 6 months follow up.
- To investigate differences in change in physical activity, lung function, exercise capacity, peripheral muscle strength and patient reported outcomes between the patients who undergo PR *before* EBV treatment versus the patients who undergo PR *after* EBV treatment between baseline and 6 months follow up.

Cardiopulmonary function:
- To investigate the effect of EBV treatment on the change in RVEDVI, and other pre-specified outcome of cardiac structure and function as measured with cardiac MRI between baseline and 8 weeks follow up.
- To investigate the relative contribution of improvement in RVEDVI to the improvement in exercise capacity or physical activity after EBV treatment between baseline and 8 weeks follow up.

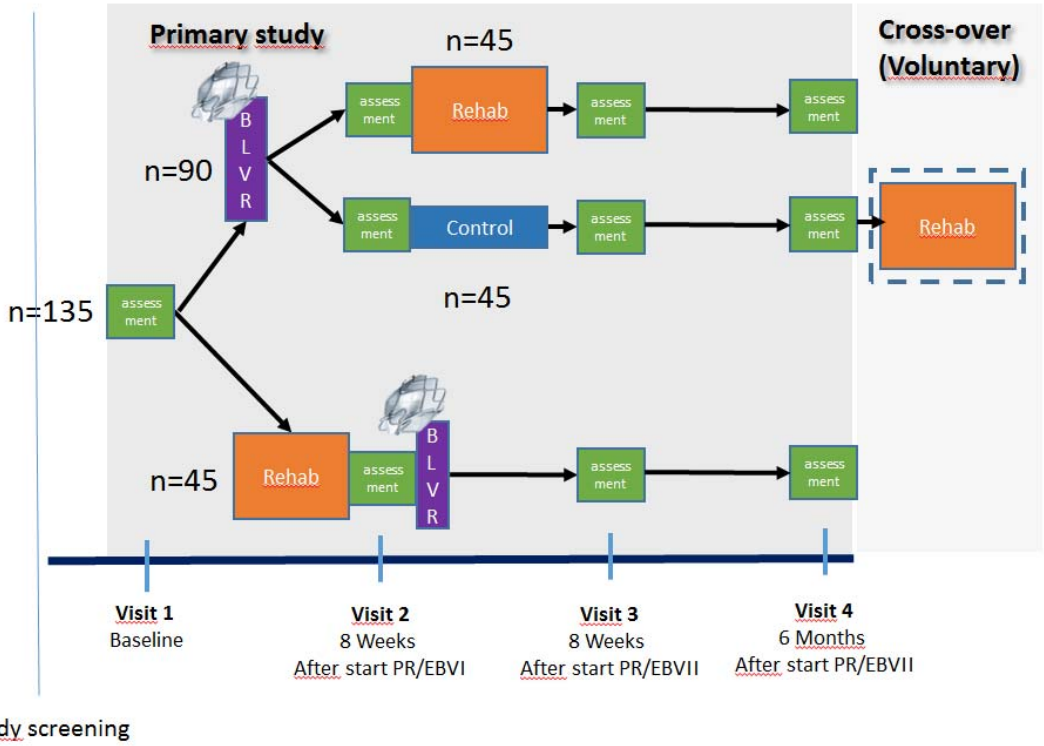
Metabolism and change in body composition
- To investigate the impact of bronchoscopic lung volume reduction on change in fat-free mass, fat mass and fat mass distribution between baseline and 8 weeks follow up..
- To investigate if there is an increase in quadriceps muscle volume after EBV treatment and whether this is related to an improvement in exercise capacity after EBV treatment between baseline and 8 weeks follow up.

- To investigate if there is an increase in cross sectional muscle area on lumbar level L1 on CT after EBV treatment and how this relates to quadriceps muscle volume between baseline and 8 weeks follow up..
- To investigate whether and to what extent the increase in quadriceps muscle volume after EBV treatment explains the variance in this improvement in exercise capacity in addition to changes in lung mechanics, and cardiac alterations between baseline and 8 weeks follow up..
- To investigate in muscle and fat biopsies before and after EBV treatment, the detailed histological and biochemical analysis of muscle fiber type composition, mitochondrial density, master regulators of muscle oxidative programming, mitochondrial respiration and lipid droplets. In addition, mRNA and protein expression of markers of inflammation and hypoxia induced signaling and (only in muscle) of regulators of muscle protein turnover.

3. STUDY DESIGN

This study is a randomized controlled trial. Patient will be randomized into 3 groups. Figure 4 shows an overview of the study design. At baseline all groups will undergo the same assessments (the measurements are described in paragraph 8.3 Study procedure). Clinical outcomes performed during a regular pre-study screening visit will be collected. In case the pre-study visit was performed more than 90 days before visit 1, tests need to be repeated. Group 1 will first follow a PR program and afterwards undergo the EBV treatment. Group 2 will first undergo the EBV treatment and approximately 8 week later will follow a PR program. Group 3 will only undergo the EBV treatment. These patient can choose whether they also want to follow a PR program after the final follow-up assessment but this is not mandatory. The follow-up assessment will take place after the completion of the first PR or 8 weeks after EBV treatment (visit 2), after the completion of the second PR or 8 weeks after EBV treatment (visit 3) and 6 months after the start of the second PR or EBV treatment (visit 4).

Figure 4. ***Overview of the study design***



The *Cardiopulmonary function* objectives only investigate the change before and after EBV and therefore will be performed in a smaller subgroup of patients. The *Metabolism and change in body composition* objectives are explorative and will only be performed in patients who wants to participate in this sub study. The sample size calculation is shown in paragraph 4.3. The cardiac MRIs will be performed in the UMCG-hospital only.

4. STUDY POPULATION

4.1 Population (base)

Patients with severe emphysema who are scheduled for a bronchoscopic lung volume reduction treatment using one-way valves.

4.2 In- and Exclusion criteria

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- COPD.
- FEV_1 ≤45%pred AND FEV_1/FVC <70%.
- TLC >100%pred AND RV>175%pred.
- CAT ≥10.
- >50% emphysema destruction @-910HU.
- >95% complete major fissure measured by quantitative CT analysis.
- Non-smoking >6 months.
- Signed informed consent.

Exclusion criteria
A potential subject who meets any of the following criteria will be excluded from participation in this study:

- PaCO2>8.0 kPa, or PaO2<6.0kPa.
- 6-minute walk test <160m.
- Significant chronic bronchitis, bronchiectasis, or other infectious lung disease.
- 3 of more hospitalizations due to pulmonary infection within last 12 months before baseline assessments
- Previous lobectomy, LVRS, or lung transplantation.
- LVEF<45% and or RVSP>50mmHg.
- Anticoagulant therapy which cannot be weaned off prior to procedure.
- Patient is significantly immunodeficient.
- Involved in other pulmonary drug studies within 30 days prior to this study.
- Pulmonary nodule which requires intervention
- Any disease or condition that interferes with completion of initial or follow-up assessments

4.3 Sample size calculation
The primary outcome parameter is the difference between the EBV group and the EBV + PR group in change in endurance time on the endurance cycle test between baseline and 6 months follow up. The minimal importance difference in cycle test endurance time is 100-105 seconds (Laviolette, 2008). To reach a power of 90%, 37 patients are needed to detect a difference of 100 (SD 130) between groups. We assume a dropout rate of approximately 20%, due to withdrawal from PR or patients who need valve removal. Therefore, 45 patients will be included per group.

Sample size calculation subgroup cardiovascular function:
The effect size chosen was extrapolated from LVRS studies (Mineo,2002). An effect size of 5 ml/m2 was selected because it was hypothesized that the changes after EBV treatment would be of a smaller magnitude to those seen after LVR surgery. Sample size calculations were based on Hudsmith ea (Hudsmith,2005). estimate of between-subject SD of 16 and assumed a 0.75 correlation between same-subject measurements of RVEDVI. Using the resulting within-subject SD of 8.13, a total of 23 patients with evaluable data from both periods would provide 80% power to detect 5ml/m2 change in RVEDVI at a two-sided significance level of 0.05. With an estimated dropout rate of 20%, 28 patients will be included.

Sample size calculation metabolic sub-objective (muscle and fat biopsies):
These analyses are explorative and therefore we are not able to perform a sample size calculation. As especially the muscle biopsies could be an invasive measurement for the patient, the patient can choose to undergo the biopsies or not. We aim for a minimum of 10 participating patients per group.

5. TREATMENT OF SUBJECTS

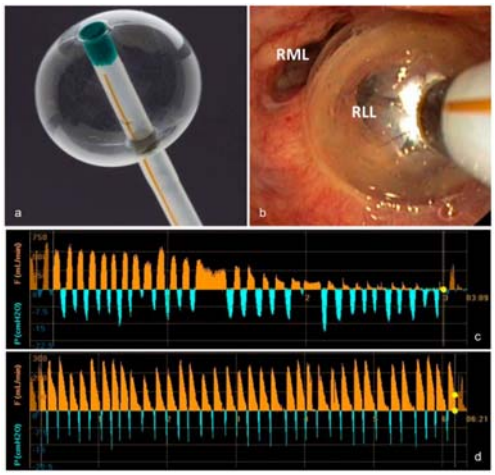
5.1 Investigational treatments

All patients in this study will undergo the EBV treatment and a Pulmonary rehabilitation program. Both treatments will be described.

EBV treatment

Before the treatment, a Chartis measurement will be performed to confirm the absence of collateral ventilation. When there is presence of collateral ventilation, patients will not be treated and the participation in this study will end.

Chartis Measurement



To achieve lung volume reduction it is crucial that there is absence of collateral ventilation between the target lobe and the adjacent lobe. While it was originally thought that airflow into and out of a lobe occurs only via the airways feeding the segment to that lobe, in 1930 Van Allen et al. observed that atelectasis did not invariably occur after blockage of the lobular bronchus, implying the presence of collateral channels in the lung (Van Allen, 1930). Temporary occlusion of an airway for the purposes of assessing air flows can be performed using a balloon catheter during bronchoscopy. The balloon temporarily occlude a lobe and the airflow from the sealed compartment is analysed. To be able to real-time measure collateral ventilation, a special system was developed, called "Chartis" (PulmonX Inc. Redwood city, CA, USA). The Chartis system is a balloon catheter-based device that allows sealing of a lung compartment and measurement of air pressure and flow from the sealed compartment. The Chartis system can measure pressure and flow and uses a balloon catheter-based system that allows temporary sealing of a lobe. The system can calculate the resistance of airflow through collateral channels and quantify the amount of collateral ventilation within a specific lobe.

The Chartis system consists of two components, the Chartis catheter and the Chartis Console. The Chartis catheter is a single- patient-use, sterile catheter with a compliant balloon component at the distal tip, designed to be inserted through the working channel of a bronchoscope. After the entrance of the target lobe is accessed by the bronchoscope, the distal tip of the catheter can be placed into the lobe, the balloon can be inflated and will temporary block the entire lobe. Air can then flow out of the target lobe into the Chartis catheter which is connected to the Chartis console. The Chartis console is an integrated system provided with software designed to measure real time airflow and pressure through the catheter and display in a graphical format. The proximal end of the Chartis catheter is attached to the Chartis console. One measurement of collateral ventilation takes approximately five minutes.

Endobronchial-Valve

The Pulmonx Zephyr Endobronchial Valve (EBV) is a device that incorporates a one-way valve that is implanted in a bronchial lumen. A stent-like self-expanding retainer that secures the implanted EBV in place supports the one-way valve. The implanted EBV is designed to allow air to be vented from the isolated lung segment while preventing air from refilling the isolated lung during inhalation.

The EBV is assembled from two distinct components: a one-way valve and a retainer.

A one-way polymer valve is mounted inside the retainer. The valve vents during exhalation and closes when flow is reversed (inhalation). The retainer is a self-expanding tubular mesh structure that is laser cut from Nitinol tubing. The retainer is covered with silicone in order to create a seal between the implant and the bronchial wall. When the EBV is delivered into the target lumen, the retainer expands to contact the walls of the bronchial lumen.

The flexible delivery catheter facilitates placement of the EBV in a targeted bronchial lumen. The delivery catheter is very similar to currently marketed tracheobronchial stent delivery catheters and will be familiar to physicians trained in the placement of airway stents. The EBV is compressed into the retractable distal housing. The EBV is deployed by actuating the deployment handle, which retracts the distal housing and releases the EBV to expand inside the target lumen. The delivery catheter can then be retracted from the EBV and removed from the patient.

Pulmonary rehabilitation program

The pulmonary rehabilitation program will consist of a state-of-the-art interdisciplinary PR program for patients with COPD consisting of 40 sessions, in line with the latest ATS/ERS Statement on Pulmonary Rehabilitation (Spruit MA (2013)). Physical exercise training is the cornerstone of the program, consisting of strengthening exercises of muscle groups of the upper and lower extremities, treadmill walking and stationary cycling. All exercises are performed at moderate to high intensity to obtain an overload stimulus. Moreover, the training intensity increased during the rehabilitation period, based on dyspnea and fatigue symptom scores. All patients undergo flexibility exercises, general physical exercise for lower and upper extremities, and endurance training. The pulmonary rehabilitation program will be performed at Beatrixoord in Haren or Ciro in Horn. Both rehabilitation programs will adjust the rehabilitation program of the individual patients to the SOP (standard operation procedure) that is developed for this trial.

5.2 Use of co-intervention

Not applicable

5.3 Escape medication

Not applicable

6. INVESTIGATIONAL PRODUCT

Not applicable

7. NON-INVESTIGATIONAL PRODUCT

Not applicable

8. METHODS

8.1 Study parameters

Main study parameter:

Primary objective:

The difference in change in endurance time measured by an endurance cycle test between the bronchoscopic lung volume reduction using endobronchial valves (EBV) treatment group and the bronchoscopic lung volume reduction + rehabilitation group (EBV+PR) between baseline and 6 months follow up.

Secondary study parameters:

Pulmonary rehabilitation

- the difference between the EBV treatment group and the EBV+PR group in change between baseline and 8 weeks and 6 months follow up (visit 3 and 4) in:
  - -Physical activity measured by accelerometry
  - -Lung function measured by spirometry, bodyplehtysmography and diffusion capacity
  - -Exercise capacity measured by an incremental cycle ergometer test and 6-minute walk distance test
  - -Peripheral muscle strength measured by a leg press test and the sit-to-stand test.
  - -Depression severity and anxiety level measured by the HADS and fatigue level measured by the CIS questionnaire.
- the differences in above mentioned variables between the patients who undergo PR *before* EBV treatment versus the patients who undergo PR *after* EBV treatment between baseline and 8 weeks and 6 months follow up (visit 3 and 4).

Patient-reported outcomes

- the change after EBV treatment in depression severity measured by the HADS questionnaire between baseline and 8 weeks and 6 months follow up (visit 3 and 4).the change after EBV treatment in anxiety level measured by the HADS questionnaire between baseline and 8 weeks and 6 months follow up (visit 3 and 4).
- the change after EBV treatment in fatigue level measured by the CIS questionnaire between baseline and 8 weeks and 6 months follow up (visit 3 and 4).

Cardiopulmonary function:

- the change after EBV treatment in RVEDVI as measured with cardiac MRI between baseline and 8 weeks follow up (visit 3).
- the change after EBV treatment in cardiac structural, volumetric, and functional changes of the right ventricle, left ventricle, and left atrium; local and regional measures of aortic

stiffness; pulmonary pulsatility as measured with cardiac MRI between baseline and 8 weeks follow up (visit 3).
- the relative contribution of improvement in RVEDVI to the improvement in exercise capacity or physical activity after EBV treatment between baseline and 8 weeks follow up (visit 3).
- the change in RVEDVI as function of actual lobar volume reduction (measured on CT and Bodyplethysmography) between baseline and 8 weeks follow up (visit 3).

Metabolism and change in body composition
- the change after EBV treatment in fat-free mass index, fat mass, and fat distribution measured by a dexa scan between baseline and 8 weeks follow up (visit 3).
- the relationship between the change in muscle volume measured on CT scan and the change in exercise capacity between baseline and 8 weeks follow up (visit 3),
- the relationship between the change in muscle volume measured on CT scan and the change in exercise capacity, change in lung mechanics (measured by HRCT and bodyplethysmography) and cardiac alteration between baseline and 8 weeks follow up (visit 3).
- In muscle and fat biopsies before and after EBV we will perform a detailed histological and biochemical analysis of muscle fiber type composition, mitochondrial density, master regulators of muscle oxidative programming, mitochondrial respiration and lipid droplets.

8.2 Randomisation, blinding and treatment allocation

Subjects will be randomized at a 1:1:1 ratio to the EBV+PR group, the PR+EBV group or the EBV alone group. The EBV alone group will have the possibility to follow a PR program after the final assessment. The randomization will take place after the pre-screening and after signing Informed consent when subjects are determined to meet the criteria to undergo the EBV treatment. Sealed envelopes with a block design will be used for the randomization. A UMCG employee who is not part of the study will perform the randomization order and create the sealed envelopes. Study personnel will not know the block size. In case a patient is CV+, the envelop will be sealed again and put at the end of the pile.

8.3 Study procedures

Before the possible treatment bronchoscopy and hospital admission patients will visit the UMCG or MUMC hospital for a second opinion consultation visit including lung function tests and HRCT scan with the pulmonary physician. When the patient is eligible for treatment, study-information will be given to the patient. Patient can let the study team know whether he/she wants to participate. The tests performed during regular visits to the hospitals related to the EBV treatment will be collected.

Flow chart of the measurements during the study

		Pre-study visit Second opinion consultation	Visit 1 Baseline ± 5 hours	Visit 2 8 week PR/EBV I ± 3 hours	Visit 3 8 week PR/EBV II ± 3 hours	visit 4 6 month PR/EBV II ± 3 hours
A	**Written Informed consent** (1)		X			
B	**Demographics, Medical History & Comorbidities**	X				
C	**Lung function**					
	Post-bronchodilator Spirometry	X		X	X	X
	Post-BD Bodyplethysmography	X		X	X	X
	Diffusion capacity	X			X	
	Arterial bloodgases	X			X	
D	**Exercise capacity/physical activity**					
	6 minute walk test	X	(X**)	X	X	X
	Cycle ergometer test (maximal) (2)		X			
	Cycle ergometer test (endurance)(2)		X	X	X	X
	Muscle strength (Microfet) (3)		X		X	X
	Muscle strength (Chair-Stand) (3)		X		X	X
	Accelerometer (4)		X		X	X
E	**Patient reported outcomes**					
	mMRC questionnaire	X		X	X	X
	CAT	X		X	X	X
	EQ-5D	X		X	X	X
	SGRQ	X		X	X	X
	Anxiety questionnaire (HADS) (5)		X	X	X	X
	Depression questionnaire (HADS)(5)		X	X	X	X
	Fatigue questionnaire (CIS)(5)		X	X	X	X
F	**Imaging**					
	HRCT*	X		X*	X*	
	Perfusion scan	X				
G	**Cardiovascular function**					
	Resting Echo cardiogram	X			X	
	SUBGROUP (UMCG)					
	Cardiac MRI (6)		X		X	
H	**Metabolism & body composition**					
	CT scan Quadriceps muscle (7)		X		X	
	Peripheral blood collection (8)		X		X	
	DEXA total body scan (9)		X		X	
	SUBGROUP (Voluntary)***					
	M. Vastus Lateralis biopsy (10)		X		X	
	Fat biopsy (11)		X		X	

* FU HRCT only performed 8 weeks after EBV treatment (not after PR treatment)

** In case patients never performed a 6MWT in the past, patients will perform 2 test to correct for a possible learning effect (according to guidelines)

*** Patients can choose to undergo the biopsies, this is voluntary

X= standard treatment related procedure

X= additional research procedure

In case the pre-study visit was performed more than 90 days before visit 1, lung function, 6-minute walk distance test and questionnaires will be repeated.

EVALUATIONS during the study (additional research procedures)

1. Signing of informed consent

Obtain a signed informed consent from the patient prior to beginning the initial screening.

2. Cycle ergometer tests

A cycle ergometer test will be performed to measure the exercise capacity of the patient. The tests will be performed according to the ATS/ACCP statement on Cardiopulmonary Exercise Testing (ATS/ERS 2002). Patients will perform an incremental maximal exercise test to determine the subject's symptom-limited peak work rate. Furthermore, patients will perform a constant work rate endurance test at a work rate adjusted to 75% of the peak work rate determined by the incremental maximal exercise test.

3. Peripheral muscle strength

Quadriceps muscle strength will be measured by a dynamometer: the MicroFET. Furthermore, muscle strength will be measured by the chair-stand test.

4. Physical activity

Daily physical activity is measured with an accelerometer; the actigraph. This device has been validated against doubly labeled water in COPD.

5. Questionnaires

The HADS and the CIS will be registered.

6. Cardiac MRI (subgroup UMCG)

Cardiac MRI imaging will be performed at before EBV treatment and 8 week after PR or EBVII treatment in a subgroup in the UMCG only. Cardiac volume and function data will be acquired according to international guidance, as described previously (Stone, 2016). Endocardial and epicardial contours will be manually segmented and summed. Aortic distensibility and pulmonary artery(PA) pulsatility will be used as measures of local arterial stiffness (Stone, 2016).

7. CT scan quadriceps muscle

A CT scan will be performed to measure the volume of the quadriceps muscle. If possible, one CT scan will be performed to measure the lungs and quadriceps.

8. Peripheral blood collection

Peripheral blood will be collected to measure systemic inflammation (HsCRP, IL-6, IL-8, TNF-alpha, TGF-beta, fibrinogen). The blood sample will be collected from all patients in the fasted state.

9. DEXA scan

Dual energy x ray absorptiometry (DEXA) will be performed to measure fat-free mass index and bone minderal density.

10. Muscle biopsies (subgroup-voluntary)

A muscle biopsy of the quadriceps muscle (vastus lateralis) will be taken from the dominant leg using the needle biopsy technique, according to the technique by Bergström et al.. The muscle biopsy will be partitioned for measurement of *ex vivo* mitochondrial function by measuring oxygen consumption polarographically using a two-chamber Oxygraph (OROBOROS Instruments), measurements of oxidative phenotype (relevant gene and protein expression levels as well as fiber type profile and enzyme activities).

11. Fat biopsies (subgroup-voluntary)

Adipose tissue biopsy SAT will be obtained paraumbilically after an overnight fast through a needle biopsy. One specimen will be snap-frozen in liquid nitrogen and stored at -80dgr. C

until further analysis, and another specimen will be processed in 4% formalin for paraffin embedding.

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

8.5 Replacement of individual subjects after withdrawal

Patients will be replaced after withdrawal until the required sample size is met.

8.6 Follow-up of subjects withdrawn from treatment

After withdrawal subject will be asked to visit the hospital for visit 4, to be able to perform an intention to treat analyses. This is voluntary. Possible reasons for withdrawal are: patients who have collateral ventilation, patient in which the valves need to be removed and voluntary withdrawal.

8.7 Premature termination of the study

The study may be terminated because of unforeseen events, adverse events or serious adverse events. This will be reported and discussed with the local METC.

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the experimental intervention. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation (a hospitalization for a secondary valve procedure is not considered a SAE);
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or

- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

The investigator will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

Follow-up of adverse events
All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

9.3 Data Safety Monitoring Board (DSMB) / Safety Committee
Since there are no risks associated with participating in this study, no DSMB or safety committee is established.

10. STATISTICAL ANALYSIS
10.1 Primary study parameter
A t-test will be performed, or Mann-Whitney in case of non-normal distribution of the data, to compare the difference in change in endurance time between the EBV group and the EBV + PR group between baseline and 6 month follow up. For all statistical analyses a p-value below 0.05 will be considered statistically significant. Besides p-values also the 95%confidence intervals will be calculated, evaluated and reported.

10.2 Secondary study parameters
A t-test will be performed, or Mann-Whitney in case of non-normal distribution of the data, to compare the difference in change in physical activity, lung function, exercise capacity, peripheral muscle strength and patient reported outcomes between the EBV group and the EBV + PR group between baseline and 8 weeks or 6 months follow up. Furthermore, also a t-test will be performed, or Mann-Whitney in case of non-normal distribution of the data, to compare the difference in change in physical activity, lung function, exercise capacity, peripheral muscle strength and patient reported outcomes between the group who undergo PR *before* EBV versus the group who perform PR *after* EBV between baseline and 8 weeks or 6 months follow up.
A paired t-test will be performed, or Wilcoxon signed rank test in case of non-normal distribution of the data, to investigate the change after EBV in patient reported outcomes, cardiopulmonary function and metabolism and changes in body composition between baseline and 8 weeks or 6 months follow up.

Univariate and multivariate regression analyses will be performed to investigate associations between the changes in the different variables. For example, the relationship between the change in muscle volume and the change in exercise capacity.
Differences in baseline variables between groups can potentially influence the absolute differences between baseline and follow up. For all variables we will check whether the baseline variables significantly differ between groups. If this is the case we will compare relative changes instead of absolute changes or will perform a multiple regression analysis with adjustment for the baseline value.

10.3 Other study parameters
Not applicable

10.4 Interim analysis
We will not perform an interim analysis.

11. ETHICAL CONSIDERATIONS
11.1 Regulation statement
This clinical investigation shall be conducted in compliance with the principles of Good Clinical Practice (GCP) guidelines, ethics committee approval and regulatory authority approval, and shall follow the guidelines as set down in the 'Declaration of Helsinki' (October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO).
The clinical investigation shall only proceed at an investigation site after the protocol and informed consent form have been approved by a duly constituted ethics committee for the centre, or equivalent institutional review board. The ethics committee shall receive a copy of the Final Report signed and dated by all relevant parties. Section B, Point No. 13. (Declaration of Helsinki) "The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol". This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which shall be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects."

11.2 Recruitment and consent
Severe emphysema patients are referrals from other pulmonologists in the Netherlands to the treating centers. Before the patient will be invited in one of the treating hospitals for a "second opinion" the referred patient data (CT scan, pulmonary function test and medical history) will be evaluated and be used as a "pre-screening" for potential treatment eligibility. If the patients seems to be eligible for a bronchoscopic lung volume reduction, we will invite the patient for a consultation with one of the lung physicians of the bronchoscopic lung volume reduction intervention team in Groningen or Maastricht. In case the patient is suitable for the EBV treatment, during this consultation the physician will inform the patient

about the treatment and provide the study-information. Afterwards, patient can let the study team know whether he/she wants to participate or not. The right of the participant to refuse to participate without giving reasons will be respected. All participants are free to withdraw at any time from the protocol without giving reasons and without prejudicing further treatment.

11.3 Objection by minors or incapacitated subjects
Not applicable

11.4 Benefits and risks assessment, group relatedness
This study has no major risks for the participating patients. The patients will be exposed to additional exercise capacity and physical activity measurements, 2 additional questionnaires, 2 CT scans of the quadriceps muscle, 2 DEXA scans and peripheral blood collection. Furthermore, a subgroup of patients will be exposed to a cardiac MRI or muscle and fat biopsies. Patient can directly benefit from the EBV treatment and the pulmonary rehabilitation program. Indirect benefit might be achieved, because, at a group level we will learn more about this novel treatment for our severe emphysema patients and will be able to further optimize this treatment.

Radiation
By taking part in this study the patient will be exposed to radiation during, during 2 CT scans of the quadriceps and during 2 DEXA scans. The estimated exposure of 1 HRCT scan is 2mSv and of 1 DEXA scan is 0,001mSv. In total the maximum estimated radiation exposure is 4,002mSv, and therefore by taking part in this study the patient will be exposed to approximately 2 years worth of natural background radiation (i.e. the same amount of natural radiation a person is exposed to from 2 years of normal living (natural radiation in the Netherlands: 2.4mSV per year (www.rivm.nl)).

Biopsies (voluntary)
Muscle and fat biopsies will be taken which can cause a local haematoma. Subjects using anti-coagulants have to stop the medication 5 days before the muscle biopsy. In case, anticoagulant therapy is mandatory, subjects will be excluded from the muscle biopsy. Infection or bleedings on the other hand are very rare. The subjects will be instructed to refrain from heavy physical labour and not to remove the pressure bandage from the leg where the biopsy was taken within the first 24h. The biopsies will be taken by a skilled medical doctor. Some subjects may also report pain during the sampling of muscle material.

11.5 Compensation for injury
The investigator has a liability insurance which is in accordance with article 7 of the WMO. The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study. The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 Incentives

Participating patients will not get paid for participating in this study. The study measurements will be performed during a regular consultation visit or an already scheduled bronchoscopy. Also there is a clearly treatment benefit. Therefore, in general participants will not receive a financial compensation for their travel costs. However, in case study measurements are performed during an extra visit, patients will receive a financial compensation for their travel costs.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

The Investigator shall permit access to all the clinical investigation data and patient source documents including original medical records by applicable regulatory authorities or appointed members of the Ethics Committees, and consent to this documentation being available for review on request. CRF will be completed for every patient and will capture all relevant patient information, including procedure observations and details of any complications or adverse reactions. The CRF will be completed by properly trained and authorized study personnel in legible writing. On completion, each CRF will be signed and dated by the investigator or study-coordinator ensuring the data accurately reflects the patient's clinical results. The clinical data in the CRF will be entered into a computerized database for secure storage, and in preparation for analysis.

Data will be handled confidentially and if possible anonymously. Where it is necessary to be able to trace data to an individual subject, a subject identification code list will be used to link the data to the subject. The code will not be based on the patient initials and birth-date. The code will be based on the number of entering in the study. For example, the first patient included in the study in the UMCG will get number 1-001. The key to the code will be safeguarded by the investigator or an independent person in case the data or human material is kept for a longer period of time. The handling of personal data will comply with the Dutch Personal Data Protection Act.

12.2 Monitoring and Quality Assurance

This study will be monitored according to GCP guidelines. A qualified and independent monitor from the UMCG and/or MUCM will be assigned to the study. This monitor is not directly involved in the study.
Data management and handling will be conducted in accordance with applicable guidelines and the standard operating procedures (SOP). The subject's personal data will be de-identified and coded. For example, the first subject included in the UMCG receives study code 1-001. During the investigation, the monitor will have regular contacts with the investigation site. The second acts will include visits to confirm that the facilities remain adequate to specified standards and that the investigation team is carrying out the procedure stated in the CIP. All data must be accurately recorded in the CRF. Source data verification (a comparison of data in the CRF with the subject's medical records and other records at the investigation site) with access to records will also be performed. The monitor will be available between visits if the Clinical Investigator or other staff at the site needs information and/or advice. Regulatory agencies may visit the site to perform

audits/inspections, including source data verification. The principal investigator will be responsible to overseeing the progress of a clinical investigation and to ensure that it is conducted, recorded, and reported in accordance with this CIP, with the monitoring manual, International Standards and the applicable regulatory requirements.

12.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

12.4 Annual progress report

The investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit. The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action. In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination. Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

12.6 Public disclosure and publication policy

Since this trial is investigator initiated, and no commercial sponsors are involved, no disclosures are warranted. Results will be published in peer reviewed journals and disseminated through national and international meetings. The publication process will be driven by the Steering Committee of this trial. Investigators can apply for data from the database by sending in a proposal with the research question and analysis plan.

13. STRUCTURED RISK ANALYSIS

This study has no major risks for the participating patients. The patients will be exposed to additional exercise capacity and physical activity measurements, 2 additional questionnaires, 2 CT scans of the quadriceps muscle, 2 DEXA scans and peripheral blood collection. In total the maximum estimated radiation exposure is 4,0mSv, and therefore by taking part in this study the patient will be exposed to approximately 2 years worth of natural background radiation. Furthermore, a subgroup of patients will be exposed to a cardiac MRI or muscle and fat biopsies.

Patient can directly benefit from the EBV treatment and the pulmonary rehabilitation program. Indirect benefit might be achieved, because, at a group level we will learn more about this novel treatment for our severe emphysema patients and will be able to further optimize this treatment.

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