Karin Klooster was born on July 2nd, 1973 in Bedum, The Netherlands. Since 1992, she works at the pulmonary department of the University Medical Center Groningen, with over 15 years of experience as a pulmonary function technician. Since 2006 she is working as clinical research coordinator in the field of bronchoscopic lung volume reduction treatments for patients with COPD. Besides working as clinical research coordinator, she started her PhD in July of 2013. She lives together with Dirk-Jan and their childeren; Marinda (17), Stijn (16), Kalena (15), Olivier (14) and Jarwin (11). She enjoys traveling, cooking, cycling and just life.

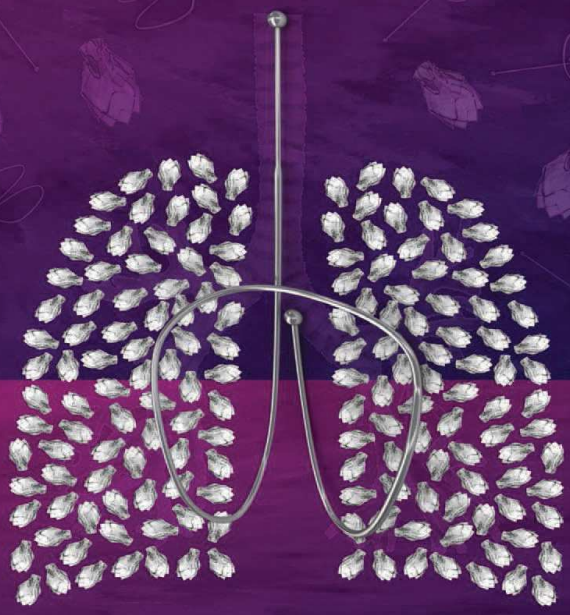
Bronchoscopic lung volume reduction

Karin Klooster

2016

Bronchoscopic lung volume reduction

A new treatment modality for patients with severe emphysema



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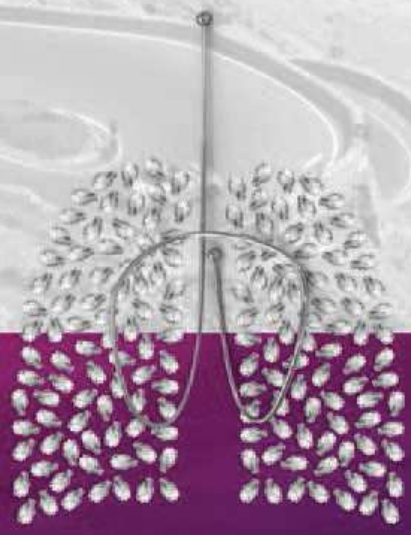

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Author: Karin Klooster
Cover design and lay-out: Karin Klooster
Printed by: Scholma Print & Media, Bedum

ISBN: 978-90-367-8773-4 (printed version)
ISBN: 978-90-367-8772-7 (electronic version)

Printing of this thesis was financially supported by:
Pulmonx Corporation; PneumRx, a BTG International group company; Holaira Inc.; CSA medical Inc.; Forbion Capital Partners; Endeavour Vision; Chiesi Pharmaceuticals B.V.; Boehringer Ingelheim B.V.; Olympus B.V.; the Graduate School of Medical Sciences of the University Medical Center Groningen and the University of Groningen.

rijksuniversiteit groningen

Bronchoscopic lung volume reduction

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Proefschrift

ter verkrijging van de graad van doctor aan de
Rijksuniversiteit Groningen
op gezag van de
rector magnificus prof. dr. E. Sterken
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

maandag 25 april 2016 om 16.15 uur

door

Henderika Klooster

geboren op 02 juli 1973

te Bedum

Promotor
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Kalena Vink

AE	Adverse event
ATS	American Thoracic Society
BLVR	Bronchoscopic lung volume reduction
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CV	Collateral ventilation
DH	Dynamic hyperinflation
DL_{CO}	Carbon monoxide diffusion capacity
EBV	Endobronchial valve
ERS	European Respiratory Society
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
HRCT	High resolution computed tomography
HU	Hounsfield units
IC	Inspiratory capacity
LVR	Lung volume reduction
LVRC	Lung volume reduction coil
LVRS	Lung volume reduction surgery
MCID	Minimal clinically important difference
MPT	Metronome paced hyperventilation
$PaCO_2$	Partial pressure of carbon dioxide
PaO_2	Partial pressure of oxygen
RAW	Airway resistance
RV	Residual volume
SAE	Serious adverse event
SD	Standard deviation
TLC	Total lung capacity
TLVR	Target lobar volume reduction
6MWD	Distance on 6 minute walk test

SGRQ	Saint George's Respiratory Questionnaire	Scores range from 0 to 100, with higher scores indicating worse quality of life.
CCQ	Clinical COPD questionnaire	Scores range from 0 to 6, with higher scores indicating worse function.
mMRC	modified Medical research council	Scores range from 0 to 4, with higher scores indicating a greater severity of dyspnea.
BMI	Body-mass index	Weight in kilograms divided by the square of the length in meters
BODE	Combination of 4 measures: Body-mass index, FEV_1 % of predicted value, mMRC score and 6MWD	Higher scores indicate higher risk of death.

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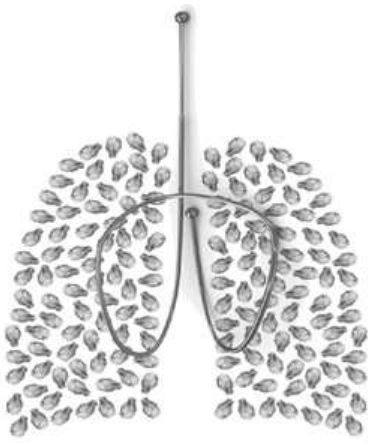
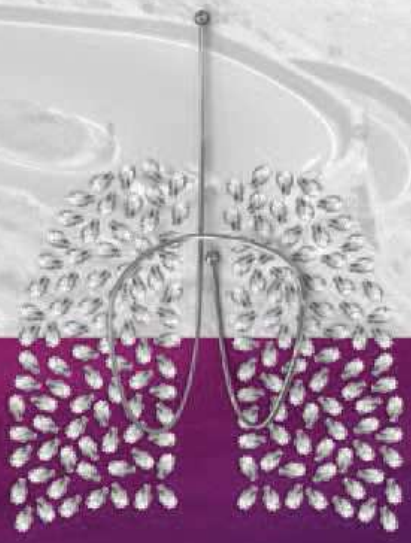


CHAPTER

1



General introduction

GENERAL INTRODUCTION

In this introduction chronic obstructive pulmonary disease (COPD), and its prevalence, symptoms, quality of life are first described as well as the currently available treatment options. In more detail, the emphysema phenotype and hyperinflation will be explained. For this latter subtype surgical treatments and new bronchoscopic treatment modalities will be introduced.

COPD

COPD is a progressive lung disease, which can be prevented and treated, but only in a symptomatic and not in curative manner. COPD is mainly caused by exogenous factors, like tobacco smoke, air pollution and indoor cooking.[1] Additionally, genetic and endogenous factors contribute to a wide variety in disease susceptibility. COPD is characterized by a spectrum of large and small airway abnormalities (the 'bronchitic/bronchiolitis' component) and by irreversible destruction of lung tissue (the 'emphysema' component). This tissue destruction leads to increased tissue elasticity and eventually results in decreased elastic recoil leading to increased airway collapse ('airway obstruction') during exhalation. These pathophysiological effects lead to so-called 'airtrapping', over time resulting in a progressive increase in lung volume, called 'hyperinflation'.

Prevalence of COPD

COPD is a major cause of chronic morbidity and mortality worldwide. According to World Health Organization estimates, 65 million people suffer from COPD and it will become the third leading cause of death by 2020.[2] The prevalence of COPD varies across countries and is much higher in smokers and ex-smokers than in non-smokers, in those with an age over 40 years than those under 40, and somewhat higher in men than in women. According to a dynamic population model for COPD, the proportional increase in prevalence and mortality between 2000 and 2025 is highest for very severe COPD. Prevalence rates of very severe COPD will increase from 5 to 13 per 10.000 inhabitants and mortality rates will increase from 1 to 2 per 10.000 inhabitants.[3] A large observational study demonstrated that approximately 70% of the patients with moderate to very severe COPD have an emphysema component based on a low-dose CT scan using a threshold of -950 Hounsfield units.[4] In The Netherlands the number of COPD patients with advanced emphysema is estimated to be approximately 5000.[5]

Symptoms and health related quality of life

The characteristic symptoms of COPD are cough, sputum production and dyspnea especially during exertion. Dyspnea is associated with disability and anxiety. Less specific symptoms can be wheezing and chest tightness. Furthermore, patients with severe to very severe COPD frequently have additional problems like fatigue, skeletal muscle dysfunction, nutritional abnormalities and weight loss. For assessing symptoms and health related quality of life, questionnaires can be used like the modified Medical Research Council Questionnaire[6] (mMRC), the St. George's Respiratory Questionnaire[7] (SGRQ); the COPD Assessment Test[8] (CAT) and the Clinical COPD Questionnaire[9] (CCQ).

Airflow obstruction

COPD is characterized by persistent airflow obstruction. Airflow obstruction is specified as a <70% ratio of the forced expiratory flow in 1 second (FEV_1)/ forced vital capacity (FVC) post-bronchodilator.[10] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) divides the severity of airflow limitation in COPD in 4 stages from mild to very severe based on the post bronchodilator FEV_1 % of the predicted value (www.goldcopd.org).[10]

The GOLD classification of the severity of airflow limitation in COPD based on post-bronchodilator measurement of FEV_1 provided the ratio of FEV_1 to FVC <70%.

		Post-bronchodilator measurement
GOLD I	mild	$FEV_1 \geq 80\%$ predicted
GOLD II	moderate	$FEV_1 \geq 50\%$ and $< 80\%$ predicted
GOLD III	severe	$FEV_1 \geq 30\%$ and $< 50\%$ predicted
GOLD IV	very severe	$FEV_1 < 30\%$ predicted

Exacerbation

A COPD exacerbation is an acute sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations leading to a change in medication.[11] Higher exacerbation frequency is associated with accelerated lung function decline, worse quality of life, and increased mortality. The best predictor so far of exacerbation risk is the individual patient's history of previous exacerbations. Two or more exacerbations in the previous year indicates higher risk.[12]

Comorbidities

Patients with COPD often have comorbidities. Frequently occurring comorbidities associated with COPD are lung cancer and other cancers, cardiovascular disease, asthma, obstructive sleep apnoea syndrome, hypertension, diabetes, metabolic syndrome, skeletal muscle dysfunction, osteoporosis, and depression.[13] In the work-up of patients with COPD an evaluation of comorbidities should be included, and comorbidities should be treated appropriately.

COPD assessment

Several assessments can be performed to determine the severity of COPD, its impact on the health condition of the patient, the risk of possible other events like an exacerbation and the presence of comorbidities. To determine the comprehensive burden and the impact of COPD on an individual patient, a combined assessment, using symptoms, breathlessness, airflow obstruction and risk of exacerbation should be performed. Based on this reasoning, the aggregate GOLD classification (GOLD A, B, C, D) reflects the complexity of COPD better than the older GOLD classification (GOLD I, II, III, IV) based on only the severity of airflow obstruction.[2]

The GOLD classification of combined COPD assessment.

		Combined assessment
GOLD A	low risk, less symptoms	Typically GOLD I or GOLD II; and/or 0-1 exacerbation per year and no hospitalization for exacerbation; CAT score < 10 or CCQ < 1 or mMRC grade 0-1
GOLD B	low risk, more symptoms	Typically GOLD I or GOLD II; and/or 0-1 exacerbation per year and no hospitalization for exacerbation; CAT score ≥ 10 or CCQ ≥ 1 or mMRC grade ≥ 2
GOLD C	high risk, less symptoms	Typically GOLD III or GOLD IV; and/or ≥ 2 exacerbations per year or ≥ 1 with hospitalization for exacerbation; CAT score < 10 or CCQ < 1 or mMRC grade 0-1
GOLD D	high risk, more symptoms	Typically GOLD III or GOLD IV; and/or ≥ 2 exacerbations per year or ≥ 1 with hospitalization for exacerbation; CAT score ≥ 10 or CCQ ≥ 1 or mMRC grade ≥ 2

Available treatments for patients with COPD

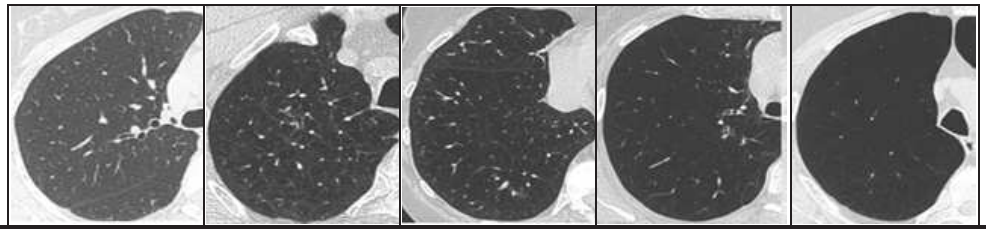
To date, there is not one single treatment available that will cure COPD. Currently, smoking cessation is the only treatment that has been demonstrated to slow down the accelerated decline in lung function in COPD, independent of previous heavy smoking, advanced age or poor baseline lung function.[14] Pharmacologic treatment, like bronchodilators and steroids, can improve symptoms, health related quality of life, exacerbation frequency and exercise capacity. This treatment needs to be patient-specific, guided by symptoms, risk of exacerbations and patient's response. Participation in a rehabilitation program can improve symptoms, quality of life, and physical and emotional participation in daily activities. Influenza and pneumococcal vaccination reduce the risk of serious illness requiring hospitalization and death in patients with COPD.[2]

Emphysema phenotypes

Emphysema is characterized by an irreversible destruction of lung tissue. A chest CT scan be used for visual assessment and scoring of lobar damage. The lung tissue destruction can be either visually assessed or objectively scored using specialized CT scan software packages. Using software, parenchymal destruction can be calculated as percentage of voxels below -910 or -950 Hounsfield units (a quantitative scale for describing radio density). The Hounsfield units used for thick slice (≥3 mm) CT data is -910 Hounsfield units[15] and the most suitable threshold for thin slice (<3 mm) CT data is -950 Hounsfield units.[16-18]

A quantitative emphysema score can be calculated for each lobe using the above described emphysema thresholds. This can be expressed as a percentage of voxels achieving the threshold, or can be converted to a 'Likert' severity scale using the conversions shown in the table below.

Overview of a quantitative emphysema score

% of lung suggestive of emphysema	0%	1-25%	26-50%	51-75%	>75%
Emphysema Likert score	0	1	2	3	4
					

To date, there is no clear definition of emphysema heterogeneity and there are multiple methods to define the heterogeneity score in the lung. A first method subtracts the emphysema score of the lower lobe from the emphysema score of the upper lobe. If there is at least one point difference in emphysema score the lung is defined as 'heterogeneous' and if there is no difference it is called 'homogeneous'. This method was used in the VENT trial.[19]

Another method to define heterogeneity assesses the absolute difference in destruction percentage between upper- and lower lobes.[20] If the emphysema distribution score between upper lobe and lower lobe is >15% than it is called 'heterogeneous' and if the difference in destruction is < 15% it is called 'homogeneous' emphysema. This method was used post-hoc in the STELVIO trial and in the feasibility trial investigating coil treatment in patients with homogeneous emphysema (both in this thesis).

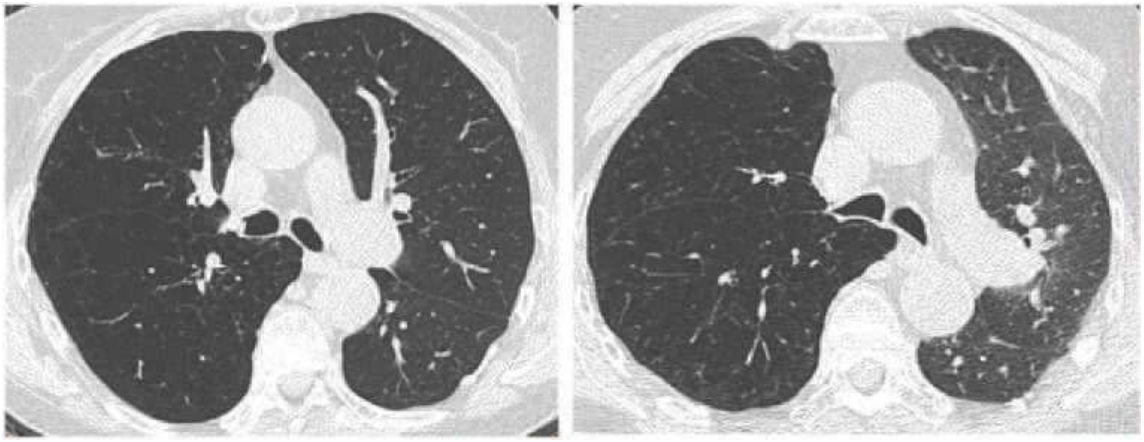
By applying the first method a patient with for example 49% (score 2) emphysema in the left upper lobe and 52% (score 3) in the lower lobe is called 'heterogeneous' (3 minus 2 = 1 point difference). The same patient is called 'homogeneous' when the second method is used (52% minus 49% = 3%). This example demonstrates the need for a uniform method to score heterogeneity.

Hyperinflation

Tissue destruction, due to emphysema, may lead to 'hyperinflation'. Hyperinflation is defined by an increase in resting end-expiratory lung volume (functional residual capacity) being accompanied by a decreased inspiratory capacity (the volume from end- of normal expiration to full inspiration). In patients with COPD the elevated resting expiratory lung volume is caused by increased airway resistance, due to airway lumen narrowing because of inflammation and airway wall thickening, and/or reduced lung elastic recoil due to alveolar destruction and emphysema. During exercise, tidal volume and respiratory rate increases resulting in a shorter expiration time. In patients with airflow obstruction this leads to a further increase in expiratory lung volume and decrease of the inspiratory capacity. This is called 'dynamic hyperinflation'.

In the figure below, high-resolution chest CT scan images are depicted at inspiration and expiration after a single lung transplantation of the left lung in an emphysema patient. The left healthy lung deflates during expiration, as it is intended to do. During expiration, there is only minor change visible in lung volume in the right emphysematous lung, compared to inspiration, indicating massive airtrapping.[21]

Inspiration **Expiration**



Patients with advanced stages of emphysema already experience dyspnea at rest, which further increases during exercise as a result of dynamic hyperinflation. Hyperinflation reduces the efficiency of the inspiratory muscles, in particular the diaphragm, and is strongly associated with increased dyspnea sensation and limited exercise capacity, both significantly reducing COPD patients' quality of life.[22]

The lack of exercise causes deconditioning, which subsequently further reduces exercise capacity and altogether severely reduces quality of life.[23] The lack of exercise causes deconditioning, which subsequently further reduces exercise capacity and altogether severely reduces quality of life.[23]

Dynamic hyperinflation can be reduced by either improving airflow during expiration or by reducing the rate of breathing to increase the time for expiration.[24] Treatment of hyperinflation theoretically leads to improvements in inspiratory capacity, exercise performance and dyspnea complaints in patients with severe COPD.

At present, bronchodilators, especially long-acting anti-muscarinics and beta$_2$-agonists, are the main pharmacologic options for improving hyperinflation by decreasing airway resistance and thereby increasing the inspiratory capacity.[25]

Pulmonary rehabilitation or exercise training reduces ventilatory drive and decreases breathing frequency during exercise, thereby resulting in improvement of hyperinflation.[26] Respiratory conditioning programs such as optimization of breathing patterns, physical therapist-assisted rib cage mobilization and improvement of body flexibility improve pulmonary symptoms and exercise endurance as well as hyperinflation.[27] Pursed-lip breathing reduces respiratory rate thereby also improving dynamic hyperinflation.[28] Supplemental oxygen and heliox breathing are other interventions that slightly reduce hyperinflation.[29]

Finally, lung volume reduction surgery in carefully selected patients reduced total lung capacity and residual volume with resultant increases in inspiratory capacity, which in turn was associated with improvements in dyspnea complaints and an increase in distance on 6 minute walk test.[22] Bronchoscopic lung volume reduction treatment might be an alternative for patients with COPD who have severe hyperinflation.

Surgical treatments

For patients with very severe COPD who receive optimal treatment, invasive surgical treatments like lung transplantation or lung volume reduction surgery can be considered.[10] Where lung transplantation might be a more definitive treatment option, it has not been definitively shown to significantly prolong survival for COPD patients worldwide, with a reported median survival of 5.5 years,[30] though it does improve quality of life. However, it is reasonable to expect survival benefit of transplantation also in patients with COPD since in our center the median survival has consistently increased over recent years, and is now above 10 years (unpublished). Furthermore, lung transplantation is only available for a very small group of patients due to both donor factors (a shortage of donor lungs), and recipient factors such as surgical fitness, biological maximal age (<65 years) and significant co-morbidity not compliant with receiving a transplant organ.[31]

Lung volume reduction surgery is the other surgical treatment option, but is only amenable in carefully selected patients with upper lobe predominant emphysema and low exercise tolerance.[32]

Lung volume reduction surgery involves resection of the most diseased and hyperinflated emphysematous tissue. It thereby reduces lung volume and allows expansion of the healthier adjacent lung and restores the outward circumferential pull on the bronchioles (i.e., increasing elastic recoil) and improving expiratory airflow and thereby improving the breathing mechanics.[32] Furthermore, the mechanical function of the diaphragm and intercostal muscles improve which results in reduced breathing effort.[33]

The improvement in breathing mechanics provided by surgical lung volume reduction is associated with significant improvements in pulmonary function, exercise performance, quality of life and survival. Unfortunately, lung volume reduction surgery is associated with acute mortality rates of 5% within 90 days as was reported in the National Emphysema Treatment Trial (NETT).[34] Since then, improvements have been made in the techniques. The 'classical' bilateral thoracotomy or sternotomy performed in the NETT trial has been changed into a less invasive unilateral video-assisted thoracoscopic surgery approach. With this new approach, the morbidity seems markedly lower than reported in the NETT trial and in one trial even without mortality within 90 days.[35] Because lung transplantation as well as lung volume reduction surgery have substantial risks, are expensive and are available to only very few selected patients. Therefore, alternative bronchoscopic treatments to achieve lung volume reduction have been developed.

New bronchoscopic treatment modalities

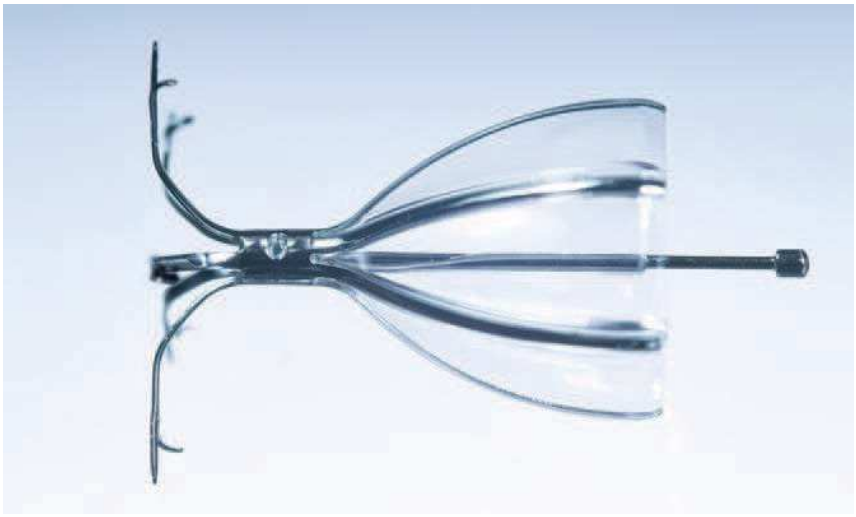
Bronchoscopic treatments
In the last decade several novel bronchoscopic treatments have been developed and are currently under investigation. These innovative bronchoscopic approaches are much less invasive compared to surgical treatments and might be applicable in a greater population of patients with very severe COPD, thereby potentially serving a big need. Currently, the two most frequently investigated bronchoscopic treatments are a so called 'blocking' device technique using 'valves' and a 'non-blocking' device technique using 'coils'. The first technique is reversible, the latter is not.

Bronchoscopic lung volume reduction treatment using valves
Bronchoscopic placement of a valve aims to block the (sub) segmental airways of the most diseased parts of the emphysematous lungs. Successful blockage should result in a full lobar atelectasis and subsequently volume reduction of the treated part of the lung, thereby mimicking lung volume reduction surgery. Valve treatment is a procedure preferably performed under general anesthesia or deep conscious sedation using a therapeutic bronchoscope with ≥ 2.8 mm working channel. At present, there are two main types of valves under investigation.

Intra bronchial valve

The intra bronchial valve (IBV™ Valve Spiration Inc., Washington, USA) is an umbrella-shaped device functioning as a one-way valve and consisting of a nickel-titanium (nitinol) frame covered with a polymer membrane and anchors that securely engage the airway walls. The valve limits airflow into the targeted airways distal to the valve but allows mucus and air movement in the proximal direction. The intra bronchial valve has been investigated in a few studies to date. In these trials the valves were placed bilaterally in the upper lobes and a partial occlusion approach (one segment of the target lobe was not treated with intra bronchial valve) was performed. However, despite a high success rate of placing the valves there were no significant improvements in lung function and exercise capacity.[36] From these initial 'intra bronchial valve' trials it was concluded that significant lung volume reduction will only be achieved when the diseased lobe is fully occluded, allowing the lobe to empty.[37] Therefore, in 2013 a large multicenter randomized controlled trial (EMPROVE study; ClinicalTrials.gov; NCT01812447) was started to investigate the safety and effectiveness of the intra bronchial valve treatment aiming at complete occlusion in patients with complete fissures.

Intra bronchial valve (IBV™ Valve Spiration Inc., Washington, USA).



Endobronchial valve

The endobronchial valve (Zephyr© Pulmonx Corporation, Redwood City, California, USA) is a self-expandable one-way valve, designed to control airflow. The device consists of a one-way, silicone, duckbill valve attached to a nitinol self-expanding retainer that is covered with a silicone membrane. It is implanted in the target bronchus using a flexible delivery catheter that is guided to the targeted bronchus by inserting it through the working channel of a bronchoscope. The technique involves the placement of one-way endobronchial valves into a single hyperinflated lobe to achieve a full lobar volume reduction and expansion of the 'healthier' adjacent lobe. The one-way valves allow expiration but block inspiration. This will gradually result in volume reduction, provided patients have no collateral ventilation between the treated lobe and the adjacent lobe(s), since this would prevent the therapeutic collapse of the lobe from happening.

In 2002 the first pilot study was performed to investigate the safety and feasibility of the endobronchial valve treatment.[38] From 2004 through to 2006, the Endobronchial Valve for Emphysema Palliation Trial (VENT) was conducted.[19] The VENT trial was a prospective, randomized, controlled study to evaluate the valve treatment in comparison with optimal medical treatment in patients with heterogeneous emphysema. It showed significant improvements in FEV_1 with the valves compared to control, but the mean improvement did not reach the minimal clinically important difference. Post-hoc analyses of the data suggested that endobronchial valve treatment might be more effective in patients characterized by a complete fissure, between the treatment target lobe and the adjacent lobe on high resolution computed tomography (HRCT) and when complete occlusion of the treatment target lobe with endobronchial valves was achieved. A complete fissure, as determined via qualitative assessment of HRCT scans, is thought to correlate with the absence of inter-lobar collateral ventilation.

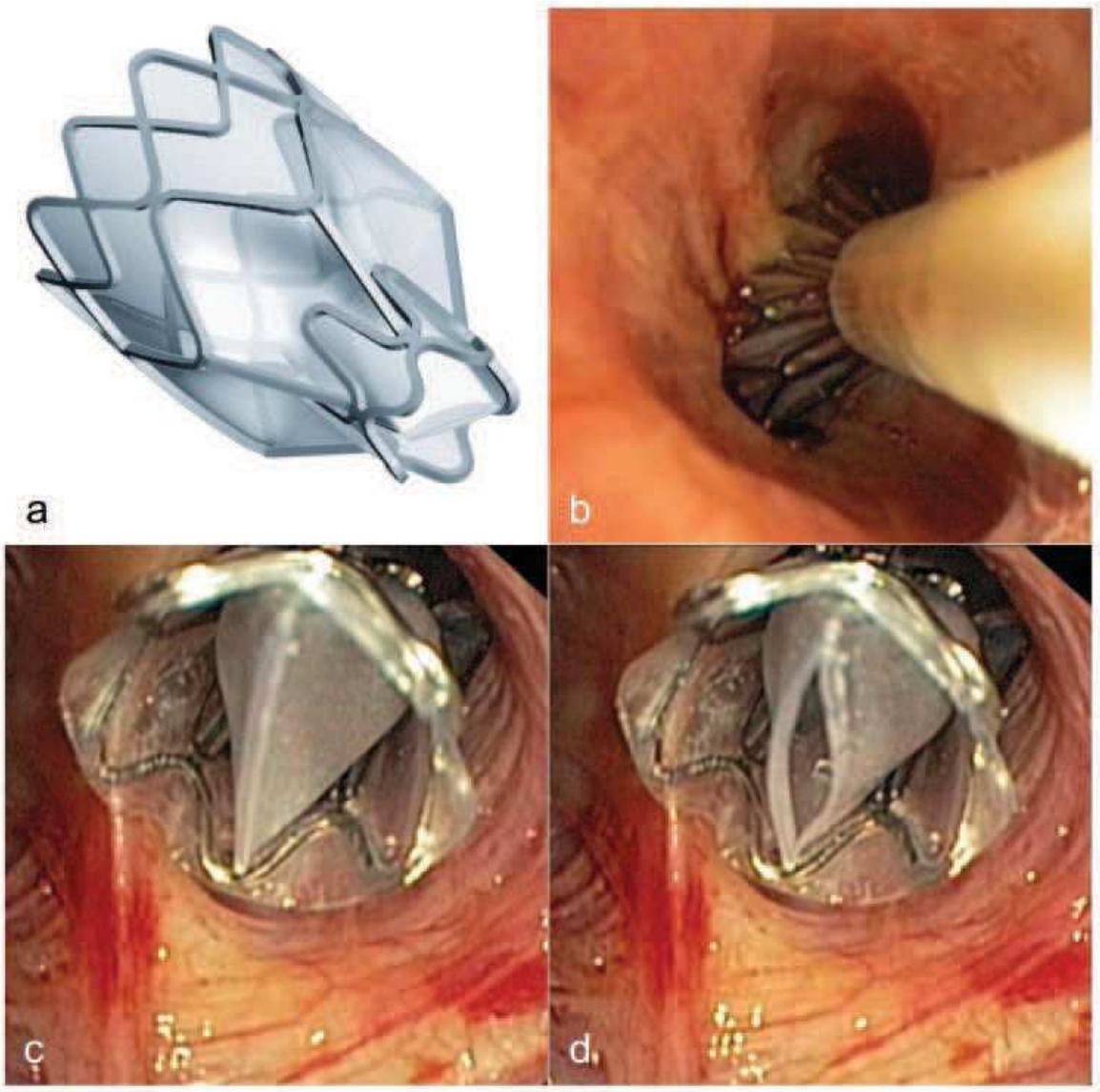
Endobronchial valve (Zephyr© Pulmonx Corporation, Redwood City, California, USA).

Endobronchial valve, 3 sizes
4.0 LP, 4.0 and 5.5

Loading cartridge

Delivery cathether

Bronchoscopic view of the endobronchial valve.[40]



(a) Endobronchial valve, cartoon

(b) Bronchoscopic view of the deployment of an endobronchial valve at the distal side just outside the delivery catheter and its placement on a distal carina, after which the endobronchial valve can be released proximally

(c) Bronchoscopic view of the endobronchial valve in situ on inspiration (valve closes to avoid inspiration of air)

(d) Bronchoscopic view of the endobronchial valve in situ during expiration (valve opens to release air)

Fissure analysis and measurement of collateral ventilation

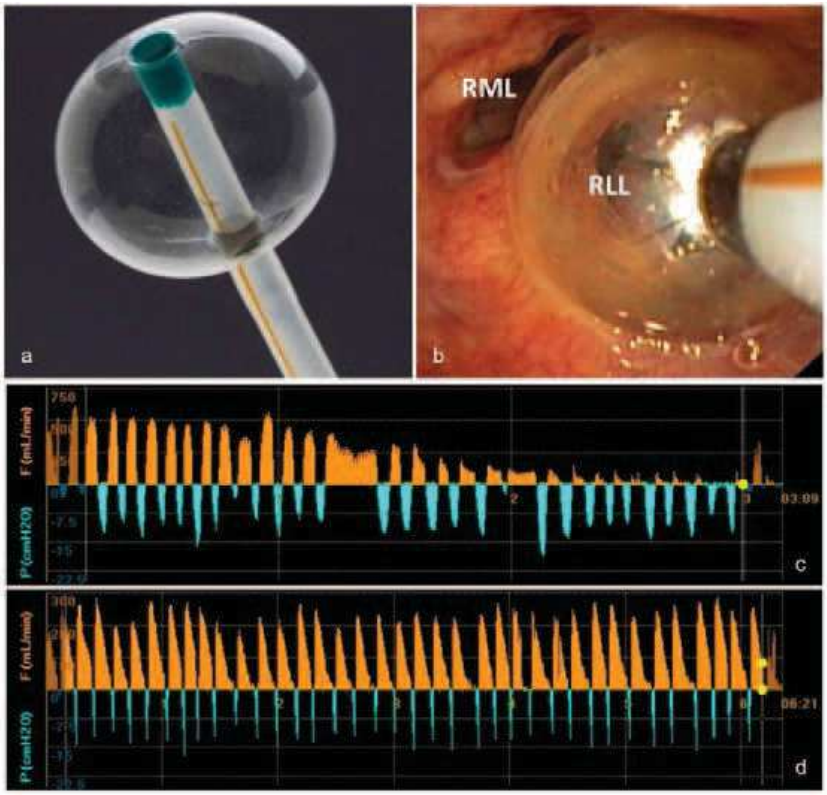
As indicated, to achieve lung volume reduction it is crucial that there is absence of collateral ventilation between the target lobe and the adjacent lobe. While it was originally thought that airflow into and out of a lobe occurs only via the airways feeding the segment to that lobe, in 1930 van Allen et al. already observed that atelectasis did not invariably occur after blockage of the lobular bronchus, implying the presence of collateral channels in the lung.[41]

The likelihood of collateral ventilation can be estimated using quantitative CT scan measures and examination of fissure integrity. Fissure integrity is defined as the completeness of the fissure on all three axis (sagittal, axial and coronal view). This is visually possible with large inter-observer variability, but more sophisticated software analysis produces more consistent results.[42] Using the CT model of intra-lobar and inter-lobar collateral ventilation can be a good alternative for effectively selecting potential patients with absence of collateral ventilation.

Besides using CT scan measures for the assessment of fissure integrity, collateral ventilation can nowadays be quantified by temporary occlusion of an airway using a balloon catheter during flexible bronchoscopy. The balloon temporarily occludes a lobe and the airflow from the sealed compartment is analysed.[43] To measure collateral ventilation real-time, a special system has been developed, called 'Chartis' (Pulmonx Corporation, Redwood City, California, USA). The system consists of a balloon catheter-based device that allows sealing of a lung compartment and measurement of air pressure and expired airflow from the sealed compartment. The system calculates whether there is residual airflow and can there with quantify the amount of collateral ventilation within a specific lobe, if it exists.

In 2010 and 2011, a prospective European multi-center study was performed to demonstrate the validity of the Chartis system.[39] The aim of the study was to identify patients who would achieve clinically significant lung volume reduction after endobronchial valve treatment. In this study the patients with little or no lobar collateral ventilation as measured by the system had significant target lobe volume reduction and significant improvements in pulmonary function, exercise performance, and quality of life measures after endobronchial valve treatment whereas those with collateral ventilation did not. This study confirmed that the assessment of collateral ventilation with the Chartis system is a safe method to predict lung volume reduction. Overall, the accuracy of the measurement for correctly predicting target lobe lung volume reduction was 75%. Therefore, the system can be used as a tool in planning endobronchial valve treatment.[39]

Representation of a Chartis measurement. [40]



(a) The catheter with at the tip a balloon.

(b) Bronchoscopic view of the balloon blocking the right lower lobe (RLL) entrance to measure collateral ventilation across the major fissure between the RLL versus the right upper lobe and right middle lobe (RML).

(c) Example image of the Chartis system registration showing an absence of collateral ventilation. The orange pattern reflects the expired airflow (ml/min) breath-by-breath. The decreasing pattern indicates no collateral ventilation. The blue pattern shows the breath-by-breath negative intrapleural pressure (cmH_2O), indicating a perfect balloon seal.

(d) Example image of the Chartis system registration showing a patent expiratory flow pattern, indicating presence of collateral ventilation.

Bronchoscopic lung volume reduction coil treatment
Lung volume reduction coil (LVR-coil) treatment is a procedure preferably performed under general anaesthesia using a therapeutic bronchoscope with ≥ 2.8 mm working channel and fluoroscopic guidance. The lung volume reduction coil procedure aims to treat two lungs, using the RePneu® Coil System (PneumRx, California, USA). A chest CT scan is used to identify target lobes in both lungs. Per procedure only one lobe is treated. About 10 coils (8–12) are placed in the upper lobes and up to 14 (10–14) can be placed in the lower lobes (this thesis[44]). During the bronchoscopic procedure self-actuating nitinol coils, are placed using a dedicate delivery system.

The hypothesised mechanism of the coil treatment is that the contraction of the most destructed lung parenchyma by the coils reduces airflow to treated portions of the lung allowing enhanced airflow to healthier untreated portions of the lung. This contraction also reduces hyperinflation, which possibly improves diaphragmatic efficiency. Additionally, by gathering up the loose parenchyma of the most severely emphysematous segments, the coil may restore elasticity and recoil to the whole lung, further improving expiratory flow rates and lessening small airway collapse with air trapping (this thesis[44]).

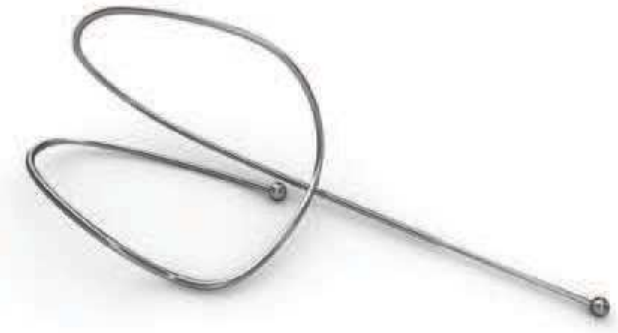
The components of the RePneu® Coil System.

Catheter

Forceps

Cartridge

Guidewire



Coil

In 2008, the first lung volume reduction coil treatment was performed in a pilot study investigating the safety and feasibility.[45] In this study the coil treatment was found to be well tolerated and feasible. However, further studies are needed to optimize the treatment, and to address the efficacy and safety of the device.

Aims and outline of this thesis

This thesis is focussed around the introduction of innovative bronchoscopic treatment modalities for patients with severe emphysema with additional attention for the role of dynamic hyperinflation.

The first aim of this thesis is to prospectively compare the endobronchial valve treatment to standard medical care as a safe and effective treatment in patients with emphysema and without collateral ventilation.

The second aim is to investigate the feasibility and efficacy of the new experimental lung volume reduction coil treatment in patients with severe emphysema.

In **chapter 2** a transthoracic endoscopic view of the impressive destructive nature of emphysema is presented. This may help to imagine why these patients suffer from severe dyspnea.

In **chapter 3** a review (in Dutch) is presented about the current bronchoscopic treatment modalities in patients with COPD. It has not been translated to facilitate reading for the general Dutch public (such as patients and non-pulmonary health care providers).

In **chapter 4** the role of dynamic hyperinflation, one of the main pathophysiological mechanisms of emphysema causing dyspnea, is determined with a manually paced test to induce dynamic hyperinflation. We assessed if dynamic hyperinflation plays an important role in exercise limitation in patients with very severe COPD.

In **chapter 5** the results of the STELVIO trial, a randomized controlled trial investigating the endobronchial valve treatment compared with standard medical care in patients without interlobar collateral ventilation, are presented.

In **chapter 6** the results of daily physical activity measurement after endobronchial valve treatment are presented.

In **chapters 7, 8, 9 and 10** the results and development of a novel bronchoscopic lung volume reduction coil treatment in patients with heterogeneous emphysema and homogeneous emphysema are presented, with a review of this data in **chapter 11.**

Chapter 12 consists of a summary of the studies presented in this thesis. in **Chapter 13** the results of the studies and future perspectives in this field are are discussed. Finally, in **Chapter 14** a summary in Dutch is presented.

References

1. Viegi G, Pistelli F, Sherrill DL, Maio S, Baldacci S, Carrozzi L. Definition, epidemiology and natural history of COPD. Eur Respir J 2007;30:993-1013.

2. Vestbo J, Hurd SS, Agusti AG, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary.
Am J Respir Crit Care Med 2013;187:347-65.

3. Hoogendoorn M, Rutten-van Molken MP, Hoogenveen RT, et al. A dynamic population model of disease progression in COPD. Eur Respir J 2005;26:223-33.

4. Coxson HO, Dirksen A, Edwards LD, et al. The presence and progression of emphysema in COPD as determined by CT scanning and biomarker expression: a prospective analysis from the ECLIPSE study. Lancet Respir Med 2013;1:129-36.

5. Hoofdstuk 2; COPD. In Longziekten, feiten en cijfers. Long Alliantie Nederland, 2013:34-47.

6. 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;54:581-6.

7. Jones PW, Quirk FH, Baveystock CM, et al. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. Am Rev Respir Dis 1992;145:1321-7.

8. Jones PW. COPD assessment test rationale, development, validation and performance.
COPD 2013;10:269-71.

9. Kocks JW, Tuinenga MG, Uil SM, et al. Health status measurement in COPD: the minimal clinically important difference of the clinical COPD questionnaire. Respir Res 2006;7:62.

10. Global Strategy for the diagnosis, management, and prevention of Chronic Obstructive Pulmonary Disease. www.goldcopd.org; 2015.

11. Burge S, Wedzicha JA. COPD exacerbations: definitions and classifications. Eur Respir J Suppl 2003;41:46s-53s.

12. Vale F, Reardon JZ, ZuWallack RL. The long-term benefits of outpatient pulmonary rehabilitation on exercise endurance and quality of life. Chest 1993;103:42-5.

13. Hillas G, Perlikos F, Tsiligianni I, Tzanakis N. Managing comorbidities in COPD.
Int J Chron Obstruct Pulmon Dis 2015;10:95-109.

14. Scanlon PD, Connett JE, Waller LA, et al. Smoking cessation and lung function in mild-to-moderate chronic obstructive pulmonary disease. The Lung Health Study.
Am J Respir Crit Care Med 2000;161:381-90.

15. Lynch DA, Al-Qaisi MA. Quantitative computed tomography in chronic obstructive pulmonary disease. J Thorac Imaging 2013;28:284-90.

16. Gevenois PA, de Maertelaer V, De Vuyst et al. Comparison of computed density and macroscopic morphometry in pulmonary emphysema. Am J Respir Crit Care Med 1995;152:653-7.

17. Gevenois PA, De Vuyst P, de Maertelaer V, et al. Comparison of computed density and microscopic morphometry in pulmonary emphysema. Am J Respir Crit Care Med 1996;154:187-92.

18. Mets OM, de Jong PA, van Ginneken B, et al. Quantitative computed tomography in COPD: possibilities and limitations. Lung 2012;190:133-45.

19. Sciurba FC, Ernst A, Herth FJ, et al. A randomized study of endobronchial valves for advanced emphysema. N Engl J Med 2010;363:1233-44.

20. Herth FJ, Noppen M, Valipour A, et al. Efficacy predictors of lung volume reduction with Zephyr valves in a European cohort. Eur Respir J 2012;39:1334-42.

21. Slebos DJ, van Rikxoort EM, van der Bij W. Air Trapping in Emphysema.
Am J Respir Crit Care Med 2015;192:e45.

22. Cooper CB. The connection between chronic obstructive pulmonary disease symptoms and hyperinflation and its impact on exercise and function. Am J Med 2006;119:21-31.

23. O'Donnell DE, Laveneziana P. Dyspnea and activity limitation in COPD: mechanical factors.
COPD 2007;4:225-36.

24. Casaburi R, Porszasz J. Reduction of hyperinflation by pharmacologic and other interventions.
Proc Am Thorac Soc 2006;3:185-9.

25. O'Donnell DE, Fluge T, Gerken F, et al. Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD. Eur Respir J 2004;23:832-40.

26. Porszasz J, Emtner M, Goto S, et al. Exercise training decreases ventilatory requirements and exercise-induced hyperinflation at submaximal intensities in patients with COPD. Chest 2005;128:2025-34.

27. Yoshimi K, Ueki J, Seyama K, et al. Pulmonary rehabilitation program including respiratory conditioning for chronic obstructive pulmonary disease (COPD): Improved hyperinflation and expiratory flow during tidal breathing. J Thorac Dis 2012;4:259-64.

28. Cabral LF, D'Elia Tda C, Marins Dde S, et al. Pursed lip breathing improves exercise tolerance in COPD: a randomized crossover study. Eur J Phys Rehabil Med 2015;51:79-88.

29. Casaburi R. Strategies to reduce dynamic hyperinflation in chronic obstructive pulmonary disease. Pneumonol Alergol Pol 2009;77:192-5.

30. Yusen RD, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirty-second Official Adult Lung and Heart-Lung Transplantation Report-2015; Focus Theme: Early Graft Failure. J Heart Lung Transplant 2015;34:1264-77.

31. Whitson BA, Hayes D,Jr. Indications and outcomes in adult lung transplantation. J Thorac Dis 2014;6:1018-23.

32. Sciurba FC, Rogers RM, Keenan RJ, et al. Improvement in pulmonary function and elastic recoil after lung reduction surgery for diffuse emphysema. N Engl J Med 1996;334:1095-9.

33. Gorman RB, McKenzie DK, Butler JE, Tolman JF, Gandevia SC. Diaphragm length and neural drive after lung volume reduction surgery. Am J Respir Crit Care Med 2005;172:1259-66.

34. Fishman A, Martinez F, Naunheim K, et al. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. N Engl J Med 2003;348:2059-73.

35. Clark SJ, Zoumot Z, Bamsey O, et al. Surgical approaches for lung volume reduction in emphysema. Clin Med 2014;14:122-7.

36. Ninane V, Geltner C, Bezzi M, et al. Multicentre European study for the treatment of advanced emphysema with bronchial valves. Eur Respir J 2012;39:1319-25.

37. Eberhardt R, Gompelmann D, Schuhmann M, et al. Complete unilateral vs partial bilateral endoscopic lung volume reduction in patients with bilateral lung emphysema. Chest 2012;142:900-8.

38. Toma TP, Hopkinson NS, Hillier J, et al. Bronchoscopic volume reduction with valve implants in patients with severe emphysema. Lancet 2003;361:931-3.

39. Herth FJ, Eberhardt R, Gompelmann D, et al. Radiological and clinical outcomes of using Chartis to plan endobronchial valve treatment. Eur Respir J 2013;41:302-8.

40. Mineshita M, Slebos DJ. Bronchoscopic interventions for chronic obstructive pulmonary disease. Respirology 2014;19:1126-37.

41. Van Allen CM, Lindskog GE, Richter HG. Gaseous Interchange Between Adjacent Lung Lobules. Yale J Biol Med 1930;2:297-300.

42. Koenigkam-Santos M, Puderbach M, Gompelmann D, et al. Incomplete fissures in severe emphysematous patients evaluated with MDCT: incidence and interobserver agreement among radiologists and pneumologists. Eur J Radiol 2012;81:4161-6.

43. Freitag L, Weise M, Linder A. Acute Response to Temporary Endoscopic Lung Volume Reduction. Chest 2004;126:709S.

44. Klooster K, Ten Hacken NH, Slebos DJ. The lung volume reduction coil for the treatment of emphysema: a new therapy in development. Expert Rev Med Devices 2014;11:481-9.

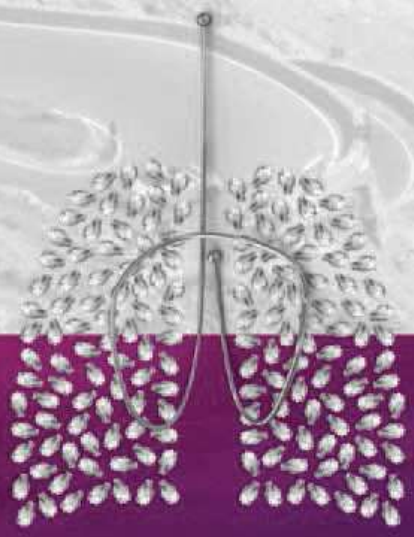
45. Herth FJ, Eberhard R, Gompelmann D, Slebos DJ, Ernst A. Bronchoscopic lung volume reduction with a dedicated coil: a clinical pilot study. Ther Adv Respir Dis 2010;4:225-31.

CHAPTER

2

Emphysema!

Dirk-Jan Slebos
Karin Klooster
Michiel Erasmus



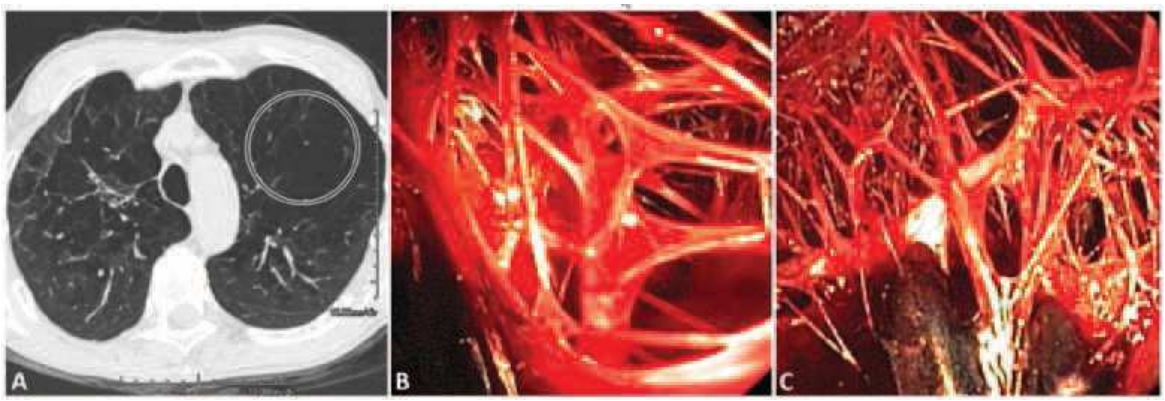
Adapted from

American Journal of Respiratory and Critical Care Medicine 2012;186:197.

Images in Pulmonary, Critical Care, Sleep Medicine and the Sciences

A 67-year-old man with end-stage emphysema characterized by severe dynamic hyperinflation was treated using an experimental minor invasive surgical technique by creating a transthoracic airway bypass from the left upper lobe to his third intercostal space, resulting in a small "pneumostoma".[1] This newly created tract easily facilitates the release of his trapped air.[2] Figures 1B and 1C (as well as the video in the online supplement) show the endoscopic evaluation (using a bronchoscope) of his "transthoracic airway bypass," where we were actually able to directly visualize the impressive destructive nature of his emphysema. These images are self-explanatory with respect to why these patients suffer from severe dyspnea. Figure 1A shows the anatomical location of the endoscopically visualized area.

Figure 1.



(A) Thoracic computed tomography scan showing severe bilateral emphysema. The circle indicates the area that was endoscopically visualized.

(B & C) Transthoracic endoscopic view of the left upper-lobe lung emphysematous parenchyma.

References

1. Saad Junior R, Dorgan Neto V, Botter M, et al. Therapeutic application of collateral ventilation with pulmonary drainage in the treatment of diffuse emphysema: report of the first three cases. J Bras Pneumol 2009;35:14–19.

2. Moore AJ, Cetti E, Haj-Yahia S, et al. Unilateral extrapulmonary airway bypass in advanced emphysema. Ann Thorac Surg 2010;89:899–906.

CHAPTER

3

Bronchoscopische interventies voor patiënten met ernstig COPD

Verbeteren van kwaliteit van leven, inspanningsvermogen en longfunctie

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Nick.H.T. ten Hacken
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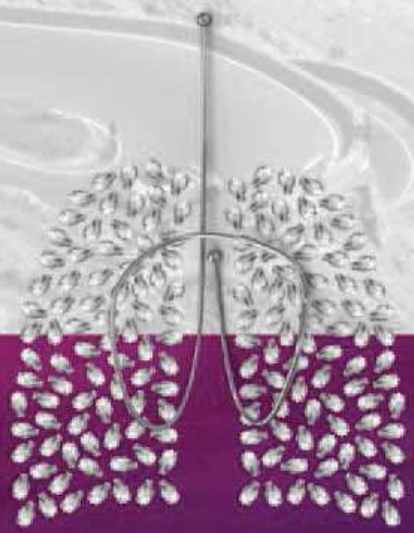


Adapted from

Nederlands Tijdschrift voor Geneeskunde 2015;159;A8497.

Kernpunten

De huidige medicamenteuze behandeling van patiënten met ernstig tot zeer ernstig COPD is vaak onvoldoende om een acceptabele kwaliteit van leven te bereiken.

Chirurgische behandeling van patiënten met COPD met longvolumereductie chirurgie of longtransplantatie is invasief en slechts voor weinig patiënten beschikbaar.

Bronchoscopische longvolumereductie is een nieuwe, minimaal invasieve, experimentele behandelmogelijkheid voor patiënten met ernstig COPD.

Afhankelijk van het type longemfyseem zijn er op dit moment 2 verschillende mogelijkheden voor behandeling: bronchoscopische interventie met eenrichtingsventielen of met longvolumereductie coils.

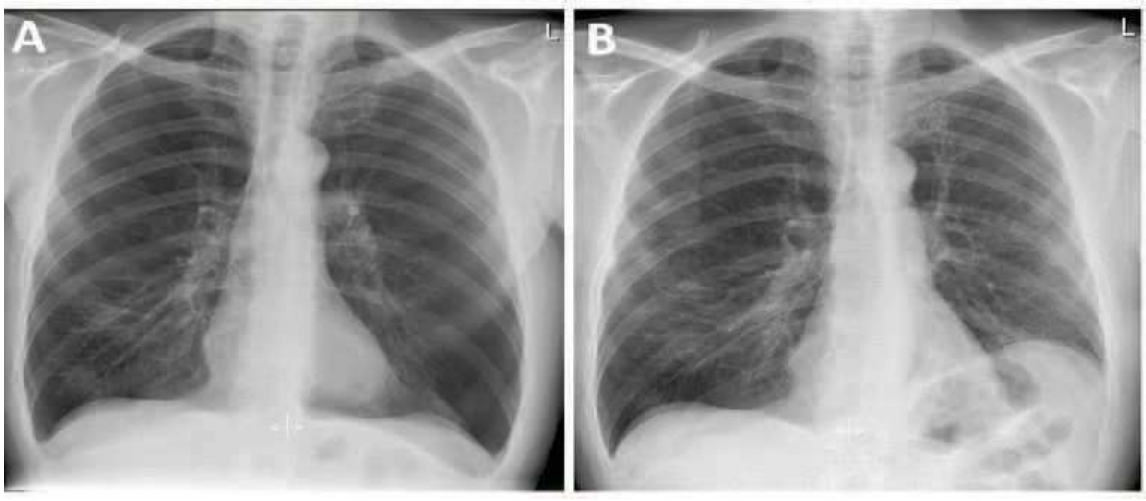
Bronchoscopische longvolumereductie zorgt bij geselecteerde patiënten met ernstig emfyseem voor een klinisch relevante verbetering in de longfunctie, het inspannings-vermogen en de kwaliteit van leven.

Gezien het innovatieve en specialistische karakter van bronchoscopische longvolume-reductie is het verstandig deze therapie uit te voeren in een COPD expertisecentrum.

Casus

Een 64-jarige man met COPD is gestopt met roken (44 jaar gerookt), heeft optimale longmedicatie, volgde een longrevalidatieprogramma en gaat 2 keer per week naar de fysiotherapeut. Toch heeft hij weinig lucht en brengt hij de dag voornamelijk zittend door. Hij is depressief en zijn kwaliteit van leven is nihil. Hij wordt naar ons verwezen voor experimentele bronchoscopische longvolumereductie. Tijdens de 6 minuten wandel test kan hij 212 meter lopen (33% van voorspeld) en is zijn geforceerde expiratoire volume in 1 seconde (FEV_1) 27% van voorspeld. Op de CT scan van de longen is uitgebreid emfyseem zichtbaar, het meest uitgesproken in de onderkwab van de linker long. Via een bronchoscoop sluiten we deze kwab volledig af met eenrichtingsventielen. Al na een paar weken is hij minder kortademig en heeft hij weer plezier in het leven. Na 1 maand loopt hij tijdens de 6 minuten wandel test 413 meter en is de FEV_1 52% van voorspeld. Op de thoraxfoto is een afname van het volume van de linker long te zien (figuur 1).

Figuur 1. Röntgenfoto's van de thorax.



(a) Voorafgaand aan bronchoscopische longvolumereductie met eenrichtingsventielen is er een hyperinflatiebeeld (ingeademd tot de 12e rib) met spaarzame longvaattekening, met name in het gebied van de linker onderkwab. (b) Na de behandeling is er een afname van het longvolume links en staat het linker hemidiafragma in een meer fysiologische positie (nu ter hoogte van de 10e rib). Door gebrek aan enig pre-existent longweefsel is de atelectase van de linker onderkwab die door de behandeling is veroorzaakt, niet te zien.

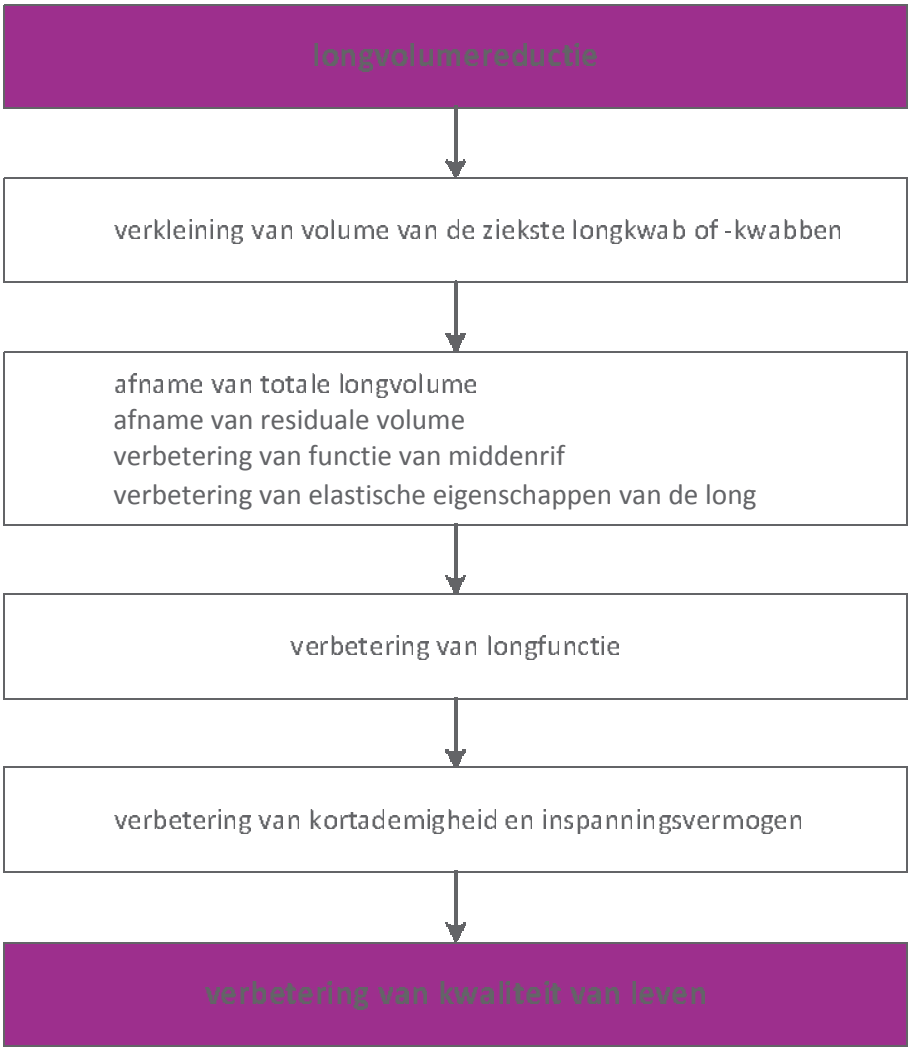
Introductie

Chronische obstructieve longziekte ('chronic obstructive pulmonary disease', COPD) is een veel voorkomende longziekte, met alleen al in Nederland meer dan 360.000 patiënten in 2007.[1] In 2011 overleden 6383 patiënten primair aan COPD, en daarmee staat deze chronische aandoening in de top 5 van doodsoorzaken in ons land.[1] COPD is een ongeneeslijke ziekte; de progressie ervan kan geremd worden door te stoppen met roken en het voorkomen en adequaat behandelen van exacerbaties.[2] Daarnaast is de behandeling vooral gericht op het verminderen van symptomen. Maximale luchtwegverwijding met inhalatiemedicatie en longrevalidatie spelen hierin een belangrijke rol. Op het moment dat er sprake is van ernstig tot zeer ernstig COPD, is er ondanks de huidige optimale behandeling weinig verbetering meer mogelijk voor deze patiënten; het aantal patiënten met ernstige tot zeer ernstig COPD in Nederland wordt geschat op 50.000.[1] Alleen bij hoge uitzondering komen deze patiënten in aanmerking voor longtransplantatie of longvolumereductie chirurgie. Voor longtransplantatie moet de patiënt in ieder geval een biologische conditie hebben die een zware chirurgische ingreep en de jarenlange intensieve immuun suppressie die daarop volgt toelaat. Er bestaat geen formele leeftijdsgrens, maar bij patiënten ouder dan 60 jaar zijn dit kritische overwegingen. Deze afwegingen samen met schaarste aan donororganen zorgen ervoor dat maar weinig patiënten behandeld kunnen worden.[3] Bij longvolumereductie chirurgie worden beide longtoppen chirurgisch verkleind. Zelfs in ervaren handen kan deze ingreep gepaard gaan met veel morbiditeit (langdurige pneumothorax, pneumonie of respiratoire insufficiëntie) en mortaliteit.[4] Bij degenen bij wie de operatie slaagt is er wel gezondheidswinst, waardoor deze therapie een duidelijke plaats inneemt in het behandel arsenaal.[5]

Bronchoscopische longvolumereductie

Voor patiënten met ernstig COPD is er dus veel ruimte voor verbetering van de huidige behandelmogelijkheden. Daarom is de afdeling Longziekten van het UMCG in 2006 begonnen met het opzetten van een programma dat specifiek is gericht op het ontwikkelen van nieuwe, niet chirurgische, minimaal invasieve technieken voor de behandeling van deze kwetsbare patiënten groep. Bij deze nieuwe behandelingen kunnen diverse soorten 'devices' bronchoscopisch worden geplaatst; dit wordt ook wel bronchoscopische longvolumereductie genoemd. Deze technieken werken min of meer analoog aan de chirurgische variant, waarbij het meest aangedane longweefsel wordt 'geofferd' ten gunste van de uitkomstmaat kwaliteit van leven van de patiënt (figuur 2).

Figuur 2. Het werkingsmechanisme van longvolumereductie.



Met chirurgische of bronchoscopische longvolumereductie wordt het slechte deel van de longen verkleind. Deze longdelen dragen in grote mate bij aan hyperinflatie en nauwelijks aan de gaswisseling. Door de volumereductie neemt het totale longvolume en het residuale volume van de longen af. Door deze volumeverandering zal het middenrif aan de behandelde kant of kanten weer in een meer fysiologische positie komen en beter kunnen functioneren. Ook verbeteren de elastische eigenschappen van de long dusdanig dat de longen weer beter kunnen ‘uitademen’. Dit proces zorgt voor een meetbare verbetering van de longfunctie. De patiënt wordt door deze verandering minder kortademig en kan zich makkelijker inspannen. Al deze veranderingen zorgen ervoor dat de patiënt zich algeheel beter voelt, wat zich vertaalt in een meetbaar betere kwaliteit van leven.

In de afgelopen jaren heeft het bronchoscopische longvolumereductie programma van het UMCG een sterke groei doorgemaakt; inmiddels zijn meer dan 300 procedures uitgevoerd, bijna allemaal in studieverband. Hoewel in Nederland nog geen reguliere vergoeding wordt verstrekt door de ziektekosten verzekeraars, is bronchoscopische longvolumereductie vaak de enig beschikbare behandeling voor deze patiënten.

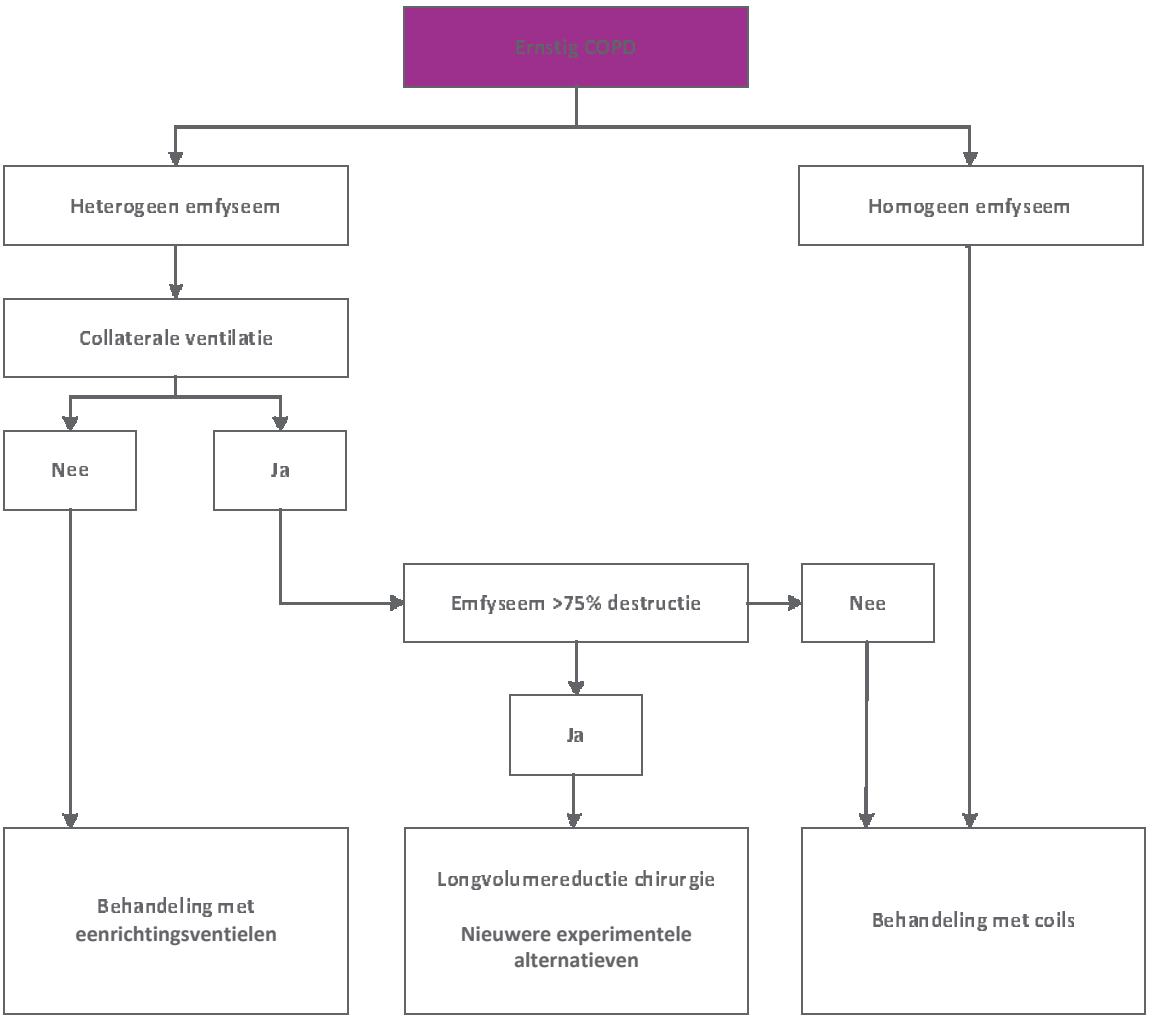
Doelgroep

De bronchoscopische longvolumereductie behandelingen die op dit moment in ontwikkeling zijn, zijn niet geschikt voor iedere patiënt met COPD. Deze vorm van behandeling wordt pas overwogen als de patiënt beperkingen blijft houden ondanks een optimale standaardbehandeling in de vorm van stoppen met roken, optimale inhalatiemedicatie en longrevalidatie, met nadien een programma bij een fysiotherapeut of sportschool. Patiënten met belangrijke co-morbiditeit, zoals frequente luchtweginfecties, hartfalen of pulmonale hypertensie, komen niet in aanmerking voor bronchoscopische longvolumereductie. Daarnaast is het belangrijk dat de patiënt met name longemfyseem heeft als uiting van COPD, en geen chronische bronchitis. De globale longfunctie criteria voor behandeling zijn: een FEV_1 ≤ 50% van de voorspelde waarde, ernstige hyperinflatie van de longen uitgedrukt als een totale long capaciteit ≥ 100% en een residuaal volume ≥ 175% van de voorspelde waarde, zoals gemeten met de bodyplethysmograaf.

Afhankelijk van de ernst, de verdeling van het emfyseem over de longen en de aanwezigheid of afwezigheid van ventilatie tussen de afzonderlijke longkwabben door incomplete fissuren (collaterale ventilatie), bestaan er op dit moment 2 verschillende mogelijkheden voor bronchoscopische longvolumereductie die dicht bij klinische implementatie staan. De CT scan analyse bepaalt hierbij de keuze (figuur 3).

In de afgelopen 10 jaar zijn verschillende devices ontwikkeld voor de uitvoering van bronchoscopische longvolumereductie. Sommige ontwikkelingen, zoals de ‘Airway bypass procedure’ en biologische longvolumereductie met ‘Aeriseal biogel’, hebben nooit het klinische stadium bereikt,[6] terwijl andere nog volop in ontwikkeling zijn.[6,7] De 2 technieken die dicht bij introductie in de klinische praktijk staan zijn: bronchoscopische interventie met eenrichtingsventielen of met longvolumereductie coils. Deze technieken zullen verder worden uitgelicht in dit artikel.

Figuur 3. Schematisch overzicht van het algoritme dat gebruikt wordt voor het maken van een keuze voor een van de huidige bronchoscopische longvolumereductie mogelijkheden voor patiënten met ernstige COPD op basis van longemfyseem.

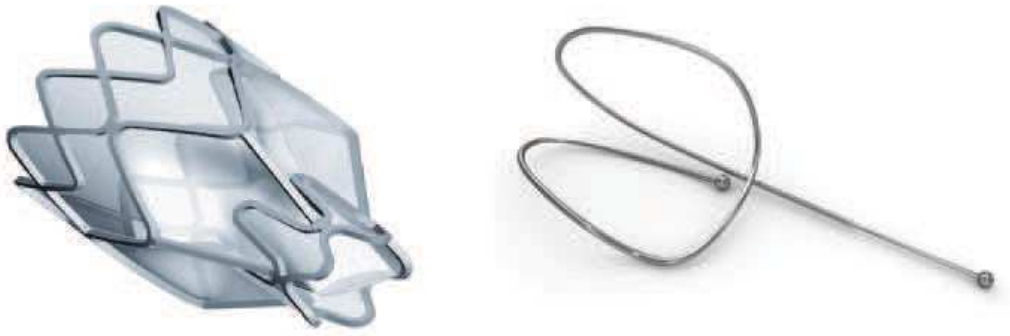


Op basis van CT scan analyse wordt beoordeeld of het emfyseem in dezelfde mate aanwezig is in de longkwabben ('homogeen emfyseem') of dat het emfyseem uitgesprokener is in de bovenkwabben of onderkwabben ('heterogeen emfyseem'), en of de fissuren intact zijn. Ook wordt de mate van destructie van het longweefsel in kaart gebracht.

Eenrichtingsventielen

Bronchoscopische longvolumereductie met eenrichtingsventielen is een bronchoscopische procedure waarbij de ingang van een longkwab met een aantal eenrichtingsventielen afgesloten wordt. Het doel van de behandeling is dat er wel lucht uit, maar geen lucht in de longkwab kan komen. Hierdoor zal de longkwab volledig ontluchten en samenvallen (atelectase). Deze atelectase zorgt voor de gewenste longvolumereductie.[8] De procedure duurt ongeveer 45 minuten en wordt uitgevoerd onder diepe sedatie of algehele anesthesie. Een eenrichtingsventiel ('endobronchial valve') is afgebeeld in figuur 4a.

Figuur 4. Een eenrichtingsventiel en een longvolumereductie coil.



(a) Eenrichtingsventiel, dat is gemaakt van een nikkeltitaniumlegering (nitinol) gecombineerd met siliconen. Het ventiel bestaat uit een zelf ontplooiend stentgedeelte, met daarin een klein ventielmechanisme op basis van het Heimlich-principe.
(b) Longvolumereductie coil van nitinol.

In 2003 werd de eerste studie gepubliceerd waarin bronchoscopisch geplaatste eenrichtingsventielen bij een kleine groep COPD patiënten succesvol waren.[9] In 2005 bleek dat deze ventielen het effectiefst zijn als er na behandeling volledige atelectase ontstaat.[10,11] Deze studies waren de aanleiding voor de 'Endobronchial valve for emphysema palliation trial' (VENT), een 'randomized controlled trial' waarin 220 COPD patiënten met heterogeen emfyseem actief behandeld werden en 101 patiënten in de controle groep zaten;[12] bij heterogeen emfyseem is het emfyseem meer uitgesproken in de bovenkwabben of onderkwabben.

De algehele resultaten van de studie waren statistisch significant maar klinisch weinig relevant, met een gemiddelde verbetering van de FEV_1 van 4.3% (95%CI: 1.4-7.2). Een post-hoc analyse toonde dat er een kleine groep patiënten was die een buitengewoon goed resultaat liet zien met een klinisch relevante en statisch significante verbetering van de FEV_1 van 16.2% (95%CI: 8.8-23.8). Deze patiënten hadden uitgesproken heterogeen emfyseem en op de CT scan was een volledig intacte fissuur zichtbaar tussen de behandelde longkwab en de aangelegen longkwab. Bij patiënten zonder intacte fissuur werd geen significante verbetering van de FEV_1 aangetoond. Volledige afsluiting van een longkwab gecombineerd met afwezige collaterale ventilatie is cruciaal voor een behandeleffect. Dat bleek ook uit onderzoek dat werd uitgevoerd met een alternatief eenrichtingsventiel, de 'intrabronchial valve'. Hiermee werd een aantal segmenten afgesloten in beide longen maar niet een gehele longkwab. De intrabronchial valve bleek op deze manier niet werkzaam.[13,14] Maar wanneer de volledige kwab wordt afgesloten, zoals bij de endobronchial valve, werkt ook de intrabronchial valve.[15]

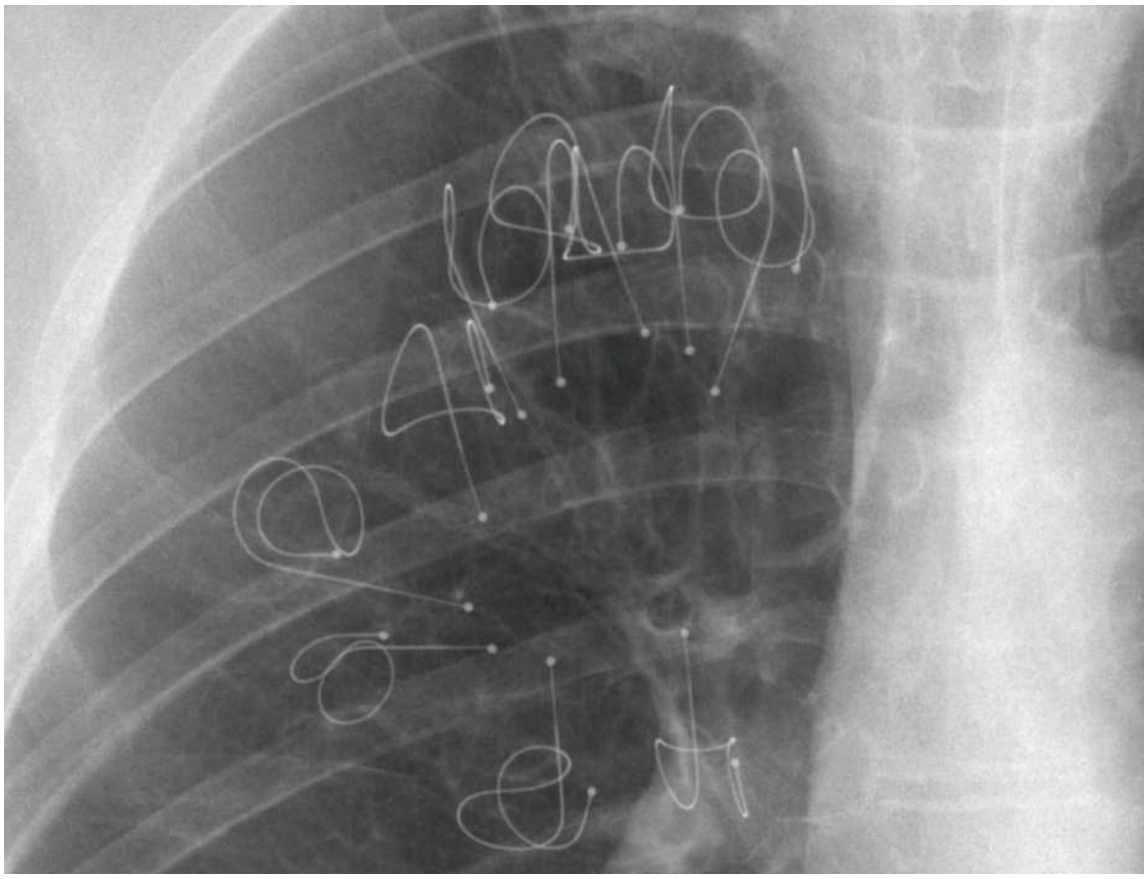
De longkwab kan alleen kleiner worden als de ingang van de longkwab volledig afgesloten wordt met eenrichtingsventielen en als er geen luchtstroom in de behandelde kwab kan komen via de aanliggende kwab (collaterale ventilatie). Het meten van aanwezigheid of afwezigheid van collaterale ventilatie kan in dezelfde procedure bronchoscopisch gemeten worden met het hiervoor speciaal ontwikkelde Chartis systeem. Met dit systeem wordt de te behandelen kwab volledig afgesloten door een ballonkatheter, terwijl tegelijkertijd zowel de druk als de luchtstroom achter de afsluiting kunnen worden gemeten. Wanneer de luchtstroom ophoudt en de negatieve druk toeneemt, is er geen sprake meer van aanvoer van lucht uit de aanliggende longkwab (collaterale ventilatie) en heeft de patiënt grote kans op een volledige ontluchting en atelectasevorming van de afgesloten kwab.[16,17] Dit zal zich vertalen in een afname van het totale longvolume en van de hyperinflatietoestand van de thorax. Behandeling met eenrichtingsventielen na een Chartis meting resulteert in een hoog percentage van responders (75%) en een belangrijke verbetering van de FEV_1 van 23±24%. Op dit moment wordt de selectie van geschikte patiënten en de behandeling met eenrichtingsventielen verder onderzocht in 2 'randomized controlled trials'.

Een mogelijk alternatief voor het functioneel uitsluiten van collaterale ventilatie met het Chartis systeem is het nauwkeurig beoordelen van de CT scan van de longen. Er moet in dat geval in 3 anatomische richtingen gekeken worden of de fissuren volledig intact zijn.[17] De meest voorkomende complicatie (ongeveer 20%) van de behandeling met eenrichtingsventielen is een pneumothorax.[18] Deze is meestal het gevolg van adhesies tussen een bullae en de pariëtale pleura, waardoor er bij de snel ontstane, maar gewenste, atelectase een scheurtje in een bullae kan ontstaan. Bij de meeste patiënten is simpele thoraxdrainage afdoende. Als de pneumothorax echter persisteert, is het tijdelijk verwijderen van een van de geplaatste ventielen voldoende voor herstel.[6-8,15,16,19]

Coils

Patiënten die niet in aanmerking komen voor bronchoscopische longvolumereductie met eenrichtings ventielen, omdat er sprake is van collaterale ventilatie of van een homogeen verdeeld emfyseem, kunnen mogelijk wel behandeld worden met longvolumereductie coils (zie figuur 3). De coil (figuur 4b) is gemaakt van een geheugenmetaal (nitinol) en wordt bronchoscopisch onder röntgendoorlichting met een speciale katheter in de luchtwegen geplaatst. In beide longen worden in de luchtwegen van de 'ziekste' longkwab 10-14 coils per longkwab ingebracht in 2 afzonderlijke procedures (figuur 5).

Figuur 5. Röntgenfoto van de thorax.



Detailopname van een röntgenfoto van de thorax met daarop 10 coils die in de subsegmenten van de rechter bovenkwab zijn geplaatst.

Deze procedure duurt ongeveer 30 minuten en wordt uitgevoerd onder algehele anesthesie. De coil zorgt er mogelijk voor dat gedestrueerd longweefsel gecomprimeerd wordt, waardoor de longelasticiteit verbetert, het overige longweefsel beter kan functioneren en kleine luchtwegen wijder worden. Dit leidt tot een afname van in de longen 'gevangen' lucht ('trapped air'), waardoor de hyperinflatie zal afnemen.

In 2009 is het eerste onderzoek bij 16 COPD patiënten verricht, bij wie beiderzijds 10 coils werden geplaatst in de bovenkwabben. Uit dit onderzoek bleek niet alleen dat plaatsing van de coil veilig uitgevoerd kon worden, maar ook dat er statistisch significante en klinisch relevante verbeteringen waren in de longfunctie, de inspanningsonderzoek parameters en de kwaliteit van leven.[20] Deze studie werd gevolgd door een prospectieve studie waarbij 11 Europese centra betrokken waren.[21] 1 jaar na de behandeling was de FEV_1 verbeterd met 0.11±0.30 Liter, het residuale volume was afgenomen met 0.71±0.81 Liter, de 6 minuten wandel afstand was toegenomen met 51±76 meter en de kwaliteit van leven zoals gemeten met de 'St. George's Respiratory' vragenlijst was verbeterd met 11±13 punten. Een kleinere gerandomizeerde studie kon deze resultaten bevestigen.[22] Een post-hoc analyse van deze gegevens suggereerde dat behandeling met coils zowel voor patiënten met heterogeen als met homogeen verdeeld emfyseem effectief is.[21] Dit kon worden bevestigd in een prospectieve studie.[23] Het is opvallend dat in al deze klinische vroege fase studies het percentage responders tussen de 50-70% ligt.[7,20-23] Deze vrij hoge respons op de behandeling wordt waarschijnlijk veroorzaakt doordat er niet alleen een longvolumereductie effect optreedt, maar mogelijk ook een vermindering van de luchtwegweerstand.[23]

De belangrijkste bijwerkingen van de coil behandeling zijn het optreden van COPD exacerbaties (tot 25%) en infectieuze complicaties (tot 10%) in de eerste paar maanden na de behandeling.[7,21] De hier beschreven onderzoeken zijn samen aanleiding geweest om 2 grotere multicentrische gerandomizeerde studies te beginnen: een studie met 100 patiënten met ernstig emfyseem (NCT01822795) en een studie met 315 patiënten met ernstig emfyseem (NCT01608490). Deze studies moeten het nut van behandeling met coils definitief onderbouwen en bijdragen aan een verfijning van de selectiecriteria.

Conclusie

Het behandelarsenaal voor patiënten met ernstig COPD bestaat uit stoppen met roken, farmacologische ondersteuning, multidisciplinaire longrevalidatie, onderhoudsbehandeling met zuurstof, en soms chirurgische longvolumereductie of long transplantatie. Sinds kort lijkt dit uitgebreid te kunnen worden met bronchoscopische longvolumereductie. Deze nieuwe techniek is bij geselecteerde patiënten met ernstig emfyseem een succesvolle behandeling. Hoewel de behandelstrategie nog volop in ontwikkeling is, lijkt deze een waardevolle aanvullende behandeling te zijn voor een patiëntengroep die op dit moment geen reëel uitzicht op enige verbetering heeft. Ernstig beperkte patiënten met emfyseem zonder belangrijke co-morbiditeit komen daarmee in aanmerking voor beoordeling op eventuele geschiktheid voor bronchoscopische longvolumereductie. Gezien het hoog specialistische karakter lijkt het vooralsnog verstandig deze therapie uit te voeren in een COPD expertisecentrum, waar deze patiënten frequent worden gezien en klinische longrevalidatie, interventiebronchoscopie, thoraxchirurgie, longtransplantatie en non-invasieve beademing onderdeel zijn van het behandelaanbod. In het UMCG beoordelen we in een multidisciplinair longpanel of patiënten in aanmerking komen voor bronchoscopische longvolumereductie. De keuze voor de optimale techniek, de technische uitvoering van de behandeling en de nazorg zijn belangrijke onderdelen van een succesvolle behandeling.

Leerpunten

Bronchoscopische longvolumereductie is een nieuwe behandeling voor patiënten met ernstig COPD; momenteel wordt deze techniek ontwikkeld en de introductie ervan in de standaardzorg voor COPD komt steeds dichterbij.

Afhankelijk van het soort emfyseem kan een patiënt worden behandeld met eenrichtingsventielen of met coils.

De belangrijkste complicaties van bronchoscopische longvolumereductie zijn een pneumothorax (met name bij eenrichtingsventielen), en COPD exacerbaties of infectieuze longproblemen (met name bij coils).

Het lijkt zinvol bronchoscopische longvolumereductie bij patiënten met ernstig COPD in een COPD expertisecentrum uit te voeren.

REFERENCES

1. COPD. In: Longziekten, feiten en cijfers 2013. Hoofdstuk 2. Amersfoort: Long Alliantie Nederland; 2013. p. 34-47.

2. Vestbo J, Hurd SS, Agustí AG, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2013;187:347-65.

3. Whitson BA, Hayes D Jr. Indications and outcomes in adult lung transplantation. J Thorac Dis. 2014;6:1018-23.

4. Ciccone AM, Meyers BF, Guthrie TJ, et al. Long-term outcome of bilateral lung volume reduction in 250 consecutive patients with emphysema. J Thorac Cardiovasc Surg. 2003;125:513-25.

5. Fishman A, Martinez F, Naunheim K, et al; National Emphysema Treatment Trial Research Group. A randomized trial comparing lungvolume- reduction surgery with medical therapy for severe emphysema. N Engl J Med. 2003;348:2059-73.

6. Mineshita M, Slebos DJ. Bronchoscopic interventions for chronic obstructive pulmonary disease. Respirology. 2014;19:1126-37.

7. Klooster K, Ten Hacken NH, Slebos DJ. The lung volume reduction coil for the treatment of emphysema: a new therapy in development. Expert Rev Med Devices. 2014;11:481-9.

8. Shah PL, Herth FJ. Current status of bronchoscopic lung volume reduction with endobronchial valves. Thorax. 2014;69:280-6.

9. Toma TP, Hopkinson NS, Hillier J, et al. Bronchoscopic volume reduction with valve implants in patients with severe emphysema. Lancet. 2003;361:931-3.

10. Hopkinson NS, Toma TP, Hansell DM, et al. Effect of bronchoscopic lung volume reduction on dynamic hyperinflation and exercise in emphysema. Am J Respir Crit Care Med. 2005;171:453-60.

11. Wan IY, Toma TP, Geddes DM, et al. Bronchoscopic lung volume reduction for end-stage emphysema: report on the first 98 patients. Chest. 2006;129:518-26.

12. 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;363:1233-44.

13. Sterman DH, Mehta AC, Wood DE, et al; IBV Valve US Pilot Trial Research Team. A multicenter pilot study of a bronchial valve for the treatment of severe emphysema. Respiration. 2010;79:222-33.

14. Ninane V, Geltner C, Bezzi M, et al. Multicentre European study for the treatment of advanced emphysema with bronchial valves. Eur Respir J.2012;39:1319-25.

15. Eberhardt R, Gompelmann D, Schuhmann M, et al. Complete unilateral vs partial bilateral endoscopic lung volume reduction in patients with bilateral lung emphysema. Chest. 2012;142:900-8.

16. Herth FJ, Eberhardt R, Gompelmann D, et al. Radiological and clinical outcomes of using Chartis™ to plan endobronchial valve treatment. Eur Respir J. 2013;41:302-8.

17. Gompelmann D, Eberhardt R, Slebos DJ, et al. Diagnostic performance comparison of the Chartis System and high-resolution computerized tomography fissure analysis for planning endoscopic lung volume reduction. Respirology. 2014;19:524-30.

18. Gompelmann D, Herth FJ, Slebos DJ, et al. Pneumothorax following endobronchial valve therapy and its impact on clinical outcomes in severe emphysema. Respiration. 2014;87:485-91.

19. Valipour A, Slebos DJ, de Oliveira HG, et al. Expert statement: pneumothorax associated with endoscopic valve therapy for emphysema; potential mechanisms, treatment algorithm, and case examples. Respiration. 2014;87:513-21.

20. Slebos DJ, Klooster K, Ernst A, et al. Bronchoscopic lung volume reduction coil treatment of patients with severe heterogeneous emphysema. Chest. 2012;142:574-82.

21. Deslee G, Klooster K, Hetzel M, et al. Lung volume reduction coil treatment for patients with severe emphysema: a European multicenter trial. Thorax. 2014;69:980-6.

22. Shah PL, Zoumot Z, Singh S, et al; RESET trial Study Group. Endobronchial coils for the treatment of severe emphysema with hyperinflation (RESET): a randomized controlled trial. Lancet Respir Med. 2013;1:233-40.

23. Klooster K, Ten Hacken NH, Franz I, et al. Lung volume reduction coil treatment in chronic obstructive pulmonary disease patients with homogeneous emphysema: a prospective feasibility trial. Respiration. 2014;88:116-25.

CHAPTER

4

Determining the role of dynamic hyperinflation in patients with severe COPD

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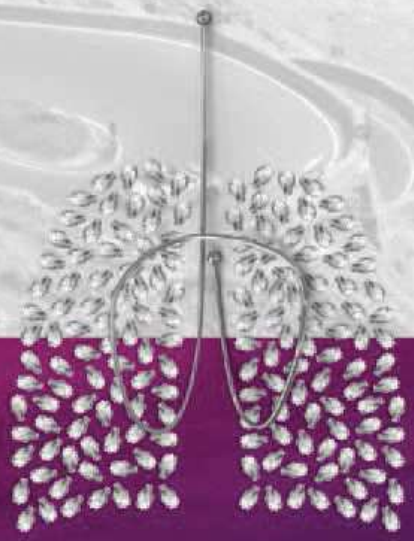


Adapted from

Respiration 2015;90:306-13.

ABSTRACT

Background
Dynamic hyperinflation due to increased respiratory frequency during exercise is associated with limitations in exercise capacity in patients with moderately severe COPD.

Objectives
The present study assessed whether the manually paced tachypnea test, sitting at rest, induces dynamic hyperinflation correlating with exercise capacity in patients with very severe COPD. Methods: Dynamic hyperinflation was induced by the manually paced tachypnea test, using a breathing frequency of 40 breaths per minute for 1 minute. Dynamic hyperinflation was defined as a 'change' in inspiratory capacity before and directly after the manually paced tachypnea test. At baseline, static hyperinflation by body plethysmography was measured, as well as the 6 minute walk test and spirometry.

Results
We studied 74 patients with severe COPD (age 59±9 years, FEV_1 28±10% of the predicted value). All patients tolerated the manually paced tachypnea test well. It induced a significant decrease in inspiratory capacity of –0.65±0.33 Liters, P<0.001, correlating with the distance on 6 minute walk test (rho= –0.246, P=0.034).

Static hyperinflation (ratio of inspiratory capacity to total lung capacity) at baseline correlated stronger with the distance on the 6 minute walk test (rho=0.582, P<0.001). Multiple regression analysis showed that static hyperinflation, but not dynamic hyperinflation, was the only independent predictor of the distance on 6 minute walk test.

Conclusion
In patients with very severe COPD, dynamic hyperinflation measurement by the manually paced tachypnea test is feasible and contributes less importantly to exercise performance than static hyperinflation.

INTRODUCTION

Dyspnea and subsequent limitation of exercise capacity are the hallmark of clinical symptoms in patients with advanced stages of COPD.[1] These symptoms can either be caused by generic factors like anxiety, muscle weakness and general fitness, or may be due to direct disease related mechanical impairments such as ventilation-perfusion mismatch or reduced lung elastic recoil and increased airway resistance leading to airflow obstruction and subsequent static and further dynamic hyperinflation.[2-7]

Static hyperinflation is defined by an increase in end-expiratory lung volume at rest being accompanied by a decreased inspiratory capacity, the volume from end expiration to full inspiration. In patients with COPD, the elevated resting end-expiratory lung volume is caused by increased airway resistance, due to airway inflammation and airway wall thickening, and/or reduced lung elastic recoil due to alveolar destruction and emphysema. This so-called static hyperinflation correlates well with several important patient-reported outcomes, such as dyspnea, poor exercise performance, and reduced quality of life.[3,4] Static hyperinflation is also an independent risk factor for mortality in subjects with COPD.[8]

Dynamic hyperinflation is defined by a further increase in end-expiratory lung volume associated with elevations in the respiratory rate, as occurs during exercise.[4] Young healthy subjects normally do not show hyperinflation during heavy exercise, but elderly subjects and particularly COPD patients, who have limitations in their expiratory flow rates, may show dynamic hyperinflation during exercise.[7,9,10] In severe COPD, this dynamic hyperinflation is superimposed on top of the already existing static hyperinflation, leading to a significantly reduced inspiratory capacity. This cumulative process of hyperinflation particularly takes place during exercise, as severely obstructed patients mainly increase their minute ventilation by increasing their breathing frequency. The increases in breathing frequency, and thus shortened expiratory time, associated with exertion in the setting of expiratory flow limitation results in progressively increasing hyperinflation, a vicious cycle leading to ventilatory limitation during exertion.[11,12]

Dynamic hyperinflation can be measured by performing inspiratory capacity maneuvers during a cycle ergometry test, but this test requires logistics, is time consuming and, most importantly, is uncomfortable for patients,[13] especially for those with very advanced stages of COPD. An alternative method to investigate the pathophysiology of dynamic hyperinflation, the so-called manually or metronome paced hyperventilation or tachypnea test, can be performed by applying a mandatory tachypnea for a short period while sitting at rest.[14,15] This test is designed to mimic the dynamic respiratory pattern that occurs during exertion, without the inconvenience of putting the subject through a progressive exercise maneuver.[12]

To date, the paced tachypnea test to investigate dynamic hyperinflation has been used predominantly in patients with mild-to-moderate COPD. The present study was designed to investigate the feasibility of the manually paced tachypnea test in patients with more severe COPD and to determine the relationship between dynamic hyperinflation and exercise capacity as assessed by the 6 minute walk test as well as quality of life.

METHODS

Study Design and Population

This was a single-center prospective cohort study in patients with severe COPD who were being evaluated for bronchoscopic lung volume reduction treatment at the Pulmonary Department of the University Medical Center Groningen, the Netherlands. All subjects were clinically stable, on optimal medication, had stopped smoking at least 6 months before the study and participated in one of our bronchoscopic lung volume reduction trials (clinical trial identifiers: NCT01421082; NCT01101958; NTR2876), which were approved by the local ethics committee, and all gave written informed consent.

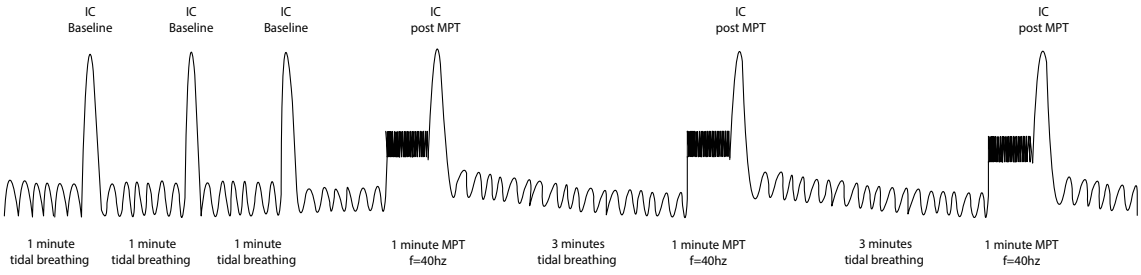
Measurements

The subjects were instructed to use their regular medications, and an additional 400 µg of salbutamol was administered 15 minutes before the pulmonary function measurements. Spirometry, body plethysmography and diffusion capacity were measured using the Jaeger MasterScreen™ body plethysmograph (CareFusion, Germany) and were performed according to the ATS/ERS guidelines[16,17] using the reference values from the European Community for Coal and Steel workers.[18] The 6 minute walk test was done according the ATS recommendations.[19] Quality of life and symptoms were measured using the St. George's Respiratory Questionnaire (SGRQ)[20,21] and the modified Medical Research Council dyspnea scale (mMRC), respectively.[22]

Measurement of Dynamic Hyperinflation

Dynamic hyperinflation was measured using a manually paced tachypnea test with the breath-by-breath method (Oxycon Pro™, CareFusion, Germany) during a 15 minute protocol (see figure 1 for a schematic overview of the manually paced tachypnea measurement).

Figure 1. Schematic overview of the manually paced tachypnea measurement.



f = Frequency (40 times in 1 minute); MPT= manually paced tachypnea test.

The subjects were given a demonstration to familiarize them with the pacing protocol. During tidal breathing, the subjects were asked to perform at least 3 slow maximum inspirations (inspiratory capacity maneuver) with a 1 minute rest in-between each. The technician then coached the subjects to increase their breathing frequency to a rate of 40 times per minute for 1 minute. The subjects were provided vocal feedback of their breathing frequency by the technician who used a computer screen displaying real-time registration of the breathing frequency. Immediately following 60 seconds of tachypnea, the subjects performed an inspiratory capacity maneuver and resumed resting tidal breathing. The manually paced tachypnea (MPT) procedure was repeated at least 3 times with a 3 minute period of resting tidal breathing between maneuvers. To obtain the baseline inspiratory capacity (IC_baseline), we calculated the mean value of 3 reproducible inspiratory capacity values (within 150 ml), and to establish the inspiratory capacity following tachypnea (IC_MPT), we calculated the mean value of the 2 highest and reproducible inspiratory capacity values (within 150 ml).[16] Pulmonary function measurements, questionnaires, 6 minute walk test and the manually paced tachypnea test were all performed on the same day.

Statistics

Data were expressed as means ± standard deviation unless otherwise indicated. A P value of <0.05 was considered statistically significant. To evaluate the variability in the repeated inspiratory capacity measurements (IC_baseline and IC_MPT), a variation coefficient was obtained by dividing the standard deviation of the inspiratory capacity measurements by the individual mean. A difference of <10% was accepted. Static hyperinflation was expressed by IC_baseline in proportion to the total lung capacity assessed by body plethysmography, thereby assuming that the total lung capacity remains constant during the manually paced tachypnea test.[10,23] Dynamic hyperinflation was calculated by the absolute change in inspiratory capacity (IC_MPT minus IC_baseline) as well as the difference (IC_MPT/total lung capacity minus IC_baseline/total lung capacity).[8] The Wilcoxon signed-ranks test was used to compare IC_baseline and IC_MPT and to compare IC_MPT/total lung capacity and IC_baseline/TLC. Pearson correlation was used to investigate univariate associations between static hyperinflation or dynamic hyperinflation and pulmonary function variables, exercise performance and quality of life when data were normally distributed. In case of non-normal distribution, Spearman correlation was used. Univariate associations with a P value <0.15 were entered in the multiple regression model. Highly correlating variables (correlation coefficient >0.75) were not entered in the model. The change in inpiratory capacity and the ratio of inspiratory capacity to total lung capacity (IC/TLC) results from the literature, shown in table 5, were either directly taken from the papers, or recalculated using the available input from these papers. IBM SPSS Statistics version 22 (IBM; Armonk, N.Y., USA) was used for all analyses.

RESULTS

Patient Characteristics

Seventy-four clinically stable patients with severe COPD (FEV_1 28±10% of the predicted value) were included between May 2010 and July 2012 (see table 1 for demographics and baseline characteristics). All subjects tolerated the manually paced tachypnea test well and were able to maintain a manually paced rate of 40 per minute (range 36–43) for 1 minute during all attempts (see table 2 for dynamic hyperinflation measurement characteristics).

Table 1. Patient demographics and baseline characteristics (N=74).

Characteristic	
Male/Female	25/49
Age, years	59±9
Smoking history, pack years	39±16
BMI, kg/m2	23.7±3.5
BODE index (N=73)	5.4±1.5
FEV1, Liter	0.77±0.32
FEV1, % of predicted value	28±10
FVC, Liter	2.53±0.83
FVC, % of predicted value	75±7
Ratio of FEV_1 to FVC, %	31±7
RV, % of predicted value	233±49
TLC, % of predicted value	136±14
Ratio of RV to TLC, %	62±9
Raw, kPa/Liter/second	0.73±0.28
Raw, % of predicted value	245±94
DL_{CO}, mmol/minute/kPa (N=63)	3.31±1.13
DL_{CO}, % of predicted value	38±12
Distance on 6 minute walk test, meter	357±92
SGRQ, points (N=73)	60.3±13.6
mMRC, points (N=73)	2.8±0.8

Results are presented as means ± standard deviation or numbers. FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; RV = residual volume; TLC = total lung capacity; Raw = airway resistance; DLCO = carbon monoxide diffusion capacity.

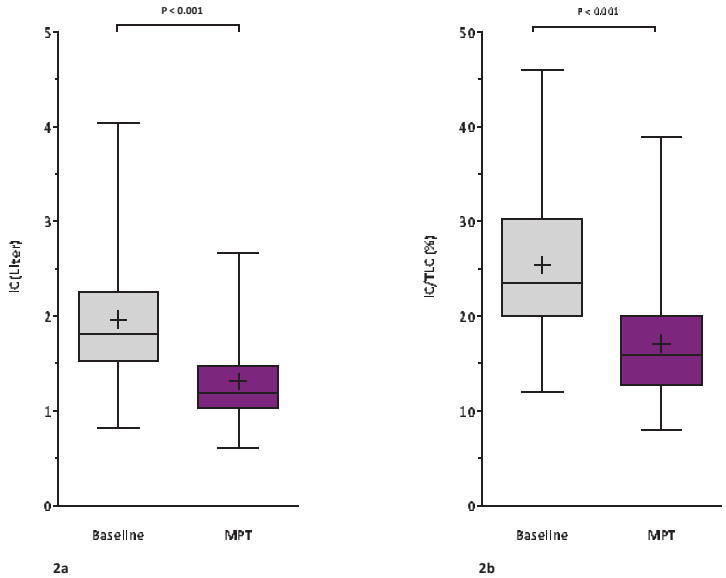
Table 2. Dynamic hyperinflation measurement characteristics (N=74).

Variables	Baseline	During MPT	P value
Breathing frequency, breaths/minute	16 (8 to 27)	40 (36 to 43)	<0.001
Tidal volume, Liter	0.75 (0.4 to 1.4)	0.54 (0.34 to 1.53)	<0.001
Ventilation, Liter/minute	12 (6 to 24)	21 (13-61)	<0.001
End tidal carbon dioxide fraction, %	4.67 (2.70 to 7.19)	3.69 (1.92 to 6.14)	<0.001
Ratio of inspiration to total time, %	34 (21 to 58)	40 (32 to 58)	<0.001

Results are presented as median (range). Difference between baseline and during manually paced tachypnea were measured with paired T-test. MPT= manually paced tachypnea.

The repeated inspiratory capacity maneuvers to establish IC_baseline and IC_MPT were reproducible showing a mean ± standard deviation variation coefficient of 4.7±0.1% and 4.3±0.1%, respectively. Immediately after the 60 seconds of tachypnea, we measured significantly lower inspiratory capacity values in all patients. In the total group, IC_baseline was 1.97±0.62 Liter and IC_MPT was 1.32±0.5 Liter. The absolute change from baseline in inspiratory capacity was –0.65±0.33 Liter(P<0.001; figure 2a). IC_baseline/TLC was 25.5±7.5% and IC_MPT/TLC was 17.1±6.2%. The absolute change from baseline in IC/TLC was –8.4±4.3% (P<0.001; figure 2b).

Figure 2. Manually paced tachypnea test results of dynamic hyperinflation.



Results presented in boxplots: median (horizontal line) and mean (+); whiskers: range. **2a.** Inspiratory capacity (IC) at baseline and directly after the manually paced tachypnea test. **2b.** Ratio of inspiratory capacity to total lung capacity (IC/TLC) at baseline and directly after the manually paced tachypnea test (MPT).

Table 3 shows the univariate associations of static hyperinflation and dynamic hyperinflation with pulmonary function tests, quality of life and exercise performance.

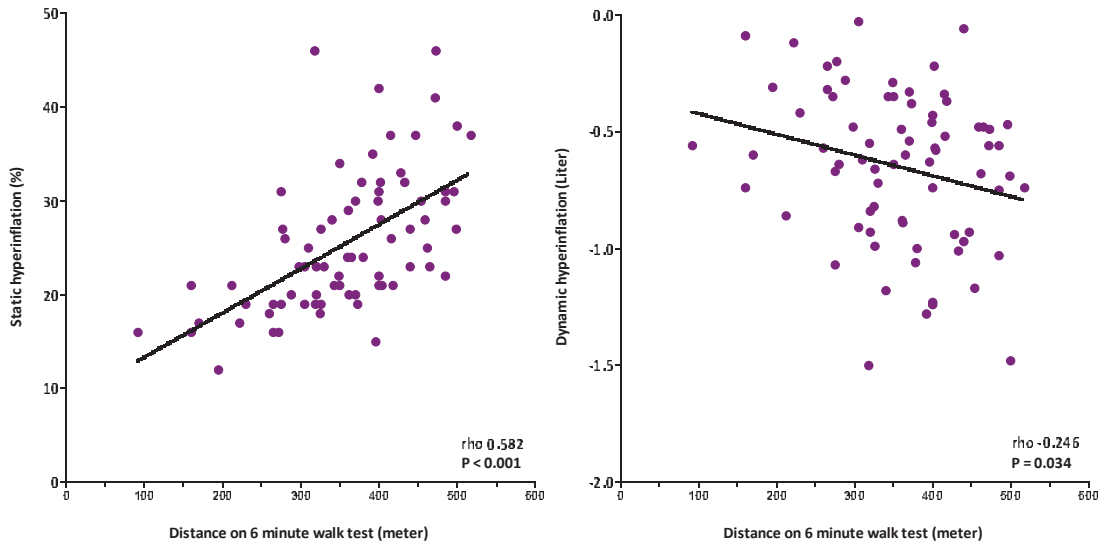
Table 3. Univariate associations between static hyperinflation and dynamic hyperinflation with pulmonary function, quality of life and exercise performance.

Variable	Static hyperinflation	P Value	Dynamic hyperinflation	P Value
VC, Liter	0.583	<0.001	-0.495	<0.001
FEV_1, Liter	0.724	<0.001	-0.343	0.003
FEV_1, % of predicted value	0.711	<0.001	-0.212	0.070
Ratio of FEV_1 to FVC, %	0.415	<0.001	0.008	0.948
RV, % of predicted value	-0.714	<0.001	0.143	0.226
TLC, % of predicted value	-0.492	<0.001	0.019	0.872
Static hyperinflation	-	-	-0.489	<0.001
Raw effective, kPa/Liter/second	-0.598	<0.001	0.182	0.121
DLCO, mmol/minute/kPa	0.399	0.001	-0.379	0.002
VE_MPT, Liter/minute	-0.612	<0.001	-0.323	0.005
6MWD, meter	0.582	<0.001	-0.246	0.034
SGRQ, points	-0.285	0.015	0.091	0.443
mMRC, points	-0.499	<0.001	0.195	0.097

Static hyperinflation: IC_baseline/total lung capacity, %; Dynamic hyperinflation: IC_MPT minus IC_baseline, Liter; VC = vital capacity; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; RV = residual volume; TLC = total lung capacity; Raw = airway resistance; DLCO = carbon monoxide diffusion capacity; VE_MPT = ventilation during manually paced tachypnea.

Static hyperinflation as expressed by the ratio of the inspiratory capacity at baseline to total lung capacity was associated with a shorter distance on the 6 minute walk test (rho=0.582, P<0.001; figure 3a) as well as with worse quality of life (SGRQ; rho= –0.285, P=0.015) and greater severity of dyspnea (mMRC; rho=–0.499, P < 0.001). Dynamic hyperinflation as defined by change in inspiratory capacity was associated with a longer distance on the 6 minute walk test (rho= –0.246, P=0.034; figure 3b), but no association was found with quality of life.

Figure 3.

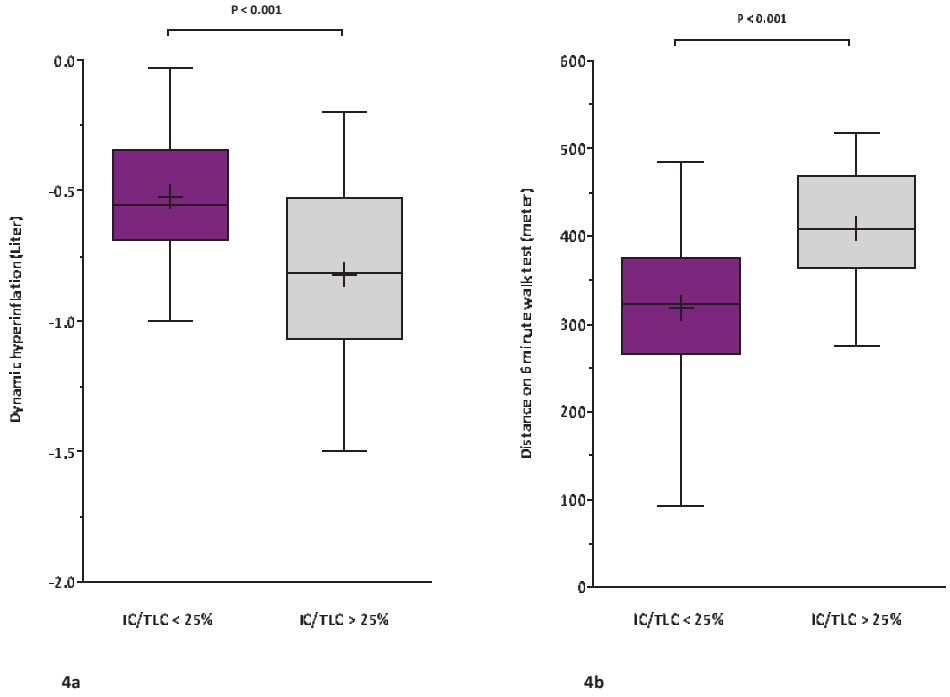


3a 3b

Static hyperinflation **(a)** and dynamic hyperinflation **(b)** associated with exercise capacity. Static hyperinflation: IC_baseline/TLC; Dynamic hyperinflation: IC_MPT minus IC_baseline.

Subjects with less severe static hyperinflation (defined as an IC_baseline/TLC ratio of >25%) showed significantly more dynamic hyperinflation, thus a greater change in inspiratory capacity (–0.82±0.35 Liter) compared to subjects with more severe static hyperinflation (defined as an IC_baseline/TLC ratio of <25%; with a change in inspiratory capacity of –0.52±0.25 Liter, P< 0.001; figure 4a). The distance on 6 minute walk test was longer in subjects with less severe static hyperinflation (distance on 6 minute walk test 409±68 meter), compared to subjects with more severe static hyperinflation (distance on 6 minute walk test 318±89 meter; P<0.001; figure 4b).

Figure 4. Comparison of IC/TLC <25% versus IC/TLC >25% with dynamic hyperinflation and the distance on 6 minute walk test.



Results presented in boxplots: median (horizontal line) and mean (+); whiskers: range. Dynamic hyperinflation: IC_MPT minus IC_baseline. (**a)** Dynamic hyperinflation in subjects with IC_baseline/TLC <25% compared to subjects with IC_baseline/TLC >25%. (**b)** Distance on 6 minute walk test in subjects with IC_baseline/TLC <25% compared to subjects with IC_baseline/TLC >25%.

The multiple regression analyses showed that the IC_baseline/TLC ratio (static hyperinflation) as well as vital capacity were independent predictors of dynamic hyperinflation (change in IC) and that static hyperinflation (IC_baseline/TLC ratio) was the only independent predictor of the distance on 6 minute walk test (table 4).

Table 4a. Multiple linear regression analyses with dynamic hyperinflation as dependent variable.

	dependent variable:	**dynamic hyperinflation**	
variable	**B**	**Standard error**	**P Value**
Vital capacity, Liter	-0.189	0.086	**0.032**
FEV_1, Liter	0.371	0.203	0.072
Static hyperinflation	-0.026	0.007	**<0.001**
Raw effective, kPa/Liter/second	0.371	0.203	0.072

Table 4b. Multiple linear regression analyses with the distance on 6 minute walk test as dependent variable.

	dependent variable:	**6MWD**	
variable	**B**	**Standard error**	**P Value**
Vital capacity, Liter	0.334	25.106	0.150
FEV_1, Liter	-0.045	58.609	0.828
Static hyperinflation	0.402	2.145	**0.024**
Raw effective, kPa/Liter/second	-0.111	46.362	0.493
Dynamic hyperinflation	-0.108	34.670	0.390

Analyses were adjusted for age, height and sex. Dynamic hyperinflation: IC_MPT minus IC_baseline. Static hyperinflation: IC_baseline/TLC. FEV_1 = forced expiratory volume in 1 second; Raw = airway resistance.

DISCUSSION

We demonstrate good feasibility for the use of the manually paced tachypnea test to induce dynamic hyperinflation in a group of patients with severe COPD. As expected, static hyperinflation was strongly associated with dyspnea rating, quality of life, several pulmonary function outcomes and poor exercise performance. While dynamic hyperinflation was associated with both dyspnea and exercise tolerance, contrary to what had been found in more mild COPD populations, there was no association with dyspnea severity or quality of life in our population. This indicates that subjects with more preserved airflow obstruction and less static hyperinflation had more dynamic hyperinflation, which was associated with better exercise capacity.

Dynamic hyperinflation was tested using the manually paced tachypnea test. The protocol used in this study was based on previously published metronome paced tachypnea protocols.[13,14,15,24] Instead of using the metronome, we chose to instruct these severe patients more personally by the technician supported by real-time monitoring of the breathing frequency. Using this approach, we achieved an average breathing frequency of 40 breaths per minute with a very small variation in the actual frequency (range 36–43 breaths per minute). Metronome or manually paced tachypnea measurements may mimic the ventilatory pattern during an exercise test in patients with severe airflow obstruction. Indeed, tidal volumes decreased during the paced tachypnea test with increasing breathing frequency being responsible for the augmentation in minute ventilation.[11,12] Although the paced tachypnea test does not exactly reflect exercise pathophysiology in this patient group, with our approach, using the manually paced tachypnea test, we achieved an average decline in inspiratory capacity of –0.65 Liters indicating that our manually paced tachypnea test is an appropriate method to test for dynamic hyperinflation.

Previous metronome paced tachypnea studies using protocols with a tachypnea period between 20 and 60 seconds and a breathing frequency of 40 breaths per minute,[13,14,15] or two times the resting breathing frequency,[2,25,26] also achieved a decline in inspiratory capacity (table 5). All previous studies were performed in a population of patients with a mainly moderate severity of COPD, and with very few severe COPD patients as represented in our study. The results in table 5 show that the magnitude of dynamic hyperinflation is hardly related to the degree of airflow obstruction, although it is problematic to compare changes in inspiratory capacity between studies, given subtle differences in the protocol and respiratory patterns achieved. Studies enrolling patients with an average FEV_1 of 1.86 Liter (65% of predicted value)[26] showed the same change in inspiratory capacity of –0.54 Liter compared with studies enrolling patients with an FEV_1 of 1.22 Liter (43% of predicted value).[14] In our population with patients who have more severe airflow obstruction, with an FEV_1 of 0.77 Liter (28% of predicted value), we even found a greater change in inspiratory capacity (–0.65 Liter). Table 5, in addition, shows that our study included patients with the lowest ratio of inspiratory capacity to total lung capacity at baseline, reflecting worse static hyperinflation.

Table 5. Literature overview of previous studies investigating the paced tachypnea test.

Author	Paced Tachypneu Method	N	FEV_1, Liter	FEV_1, % of predicted value	Ratio of IC to TLC, %	Delta IC, Liter
Hannink[25]	2 x BF rest	68	1.61±0.07	56±2	-	-0.62±0.04
Lahije[26]	2 x BF rest	45	1.86±0.73	65±24	37*	-0.54*
Cooper[24]	40 Hz	35	1.76±0.5	59±9	37*	-0.36±0.05
Calligaro[13]	40 Hz	24	1.70±0.45	59±9	37*	-0.37±0.30
Gelb[2]	2 x BF rest	16	1.63±0.53	60*	39*	-0.39±0.29
Lahije[28]	2 x BF rest	53	1.60±0.6	58±22	38*	-0.53*
Fuijmoto[15]	40 Hz	59	-	54*	-	-0.32±0.03
Weigt[14]	40 Hz	14	1.22±041	43±14	30±11	-0.54
Current study	40 Hz	74	0.77±0.32	28±10	25.5±7.5	-0.65±0.33

Data are presented as means ± standard deviation or in numbers. *Standard deviation value is not available. BF = breathing frequency.

How can we explain that our very severe COPD patients revealed the highest change in inspiratory capacity in the literature, yet a negative correlation with disease severity within the study? We hypothesize that dynamic hyperinflation during tachypnea may progress differently with increasing severity of airway obstruction and static hyperinflation. Young individuals without airway obstruction routinely lower their end-expiratory lung volume and thus increase their inspiratory capacity during exertion. By contrast, aging individuals and those who progress from minimally to moderately obstructed will elevate their end-expiratory lung volume and decrease their inspiratory capacity.[23,27,28] Finally, individuals who have progressed to very severe airway obstruction like in our study frequently have an already hyperinflated state at rest. Such individuals have little capacity to further increase their elevated end-expiratory lung volume, and consequently show only modest decreases in inspiratory capacity. In our study, we included mainly very severe COPD patients, and, therefore, we were able to demonstrate a negative correlation between dynamic hyperinflation and disease severity. Future studies might also include a comparative group of less severe COPD patients.

As expected, we found a strong inverse correlation between static hyperinflation and exercise performance.[3,4] Contrary to our expectations, however, we observed that a greater dynamic hyperinflation as reflected by a greater reduction in inspiratory capacity was associated with a longer distance on the 6 minute walk test. This finding contrasts with observations in previous studies, which included mainly moderate COPD patients.[29] These previous studies demonstrated that the presence or magnitude of dynamic hyperinflation was either unrelated to exercise endurance and dyspnea[13,28] or that dynamic hyperinflation was associated with a decline in physical activity.[29] In our population with severe COPD patients, 57% of these patients had a ratio of inspiratory capacity to total lung capacity below 25%,[8] reflecting more severe static hyperinflation.

These individuals thus have very little capacity to decrease their inspiratory capacity even further during the manually paced tachypnea test or during exercise. Interestingly, the distance on 6 minute walk test correlated significantly with both static and dynamic hyperinflation; however, the correlation was stronger with static hyperinflation, and static hyperinflation was the only independent predictor of the distance on 6 minute walkt test in a multiple regression model. We believe that the observed negative association between dynamic hyperinflation and the distance on 6 minute walk test is attributable to the greater disease severity of our population and the associated severe static hyperinflation.

CONCLUSION

The 15 minute manually paced tachypnea test is a feasible procedure to study dynamic hyperinflation in patients with severe COPD. Static hyperinflation in this severe group seems to be a more important contributor to limited exercise performance and poor quality of life than dynamic hyperinflation. Based on the data of this study, static hyperinflation seems to be a better predictor of exercise performance than dynamic hyperinflation. The negative correlation between the static and dynamic hyperinflation reflects the reduced capacity of very severe COPD patients to increase their already elevated static hyperinflation. Measurements of inspiratory capacity or change in inspiratory capacity in this group made during dynamic maneuvers do not further contribute to an understanding of their exercise or functional limitations, in contrast to such observations made in patients with mild and moderate airway obstruction.

Acknowledgments

The authors would like to thank the pulmonary function technicians Marga Star, Yvonne Valkema, Maria Heuving and Margrietha Swierenga for their dedicated testing and Martijn Farenhorst for his technical support; Ruth Hiltermann for performing the 6 minute walk tests and obtaining questionnaires, and Judith Hartman for drawing figure 1.

REFERENCES

1. O'Donnell DE, Laveneziana P: Dyspnea and activity limitation in COPD: mechanical factors. COPD 2007; 4: 225–236.

2. Gelb AF, Gutierrez CA, Weisman IM, Newsom R, Taylor CF, Zamel N: Simplified detection of dynamic hyperinflation. Chest 2004; 126: 1855–1860.

3. Cooper CB: Airflow obstruction and exercise. Respir Med 2009; 103: 325–334.

4. Cooper CB: The connection between chronic obstructive pulmonary disease symptoms and hyperinflation and its impact on exercise and function. Am J Med 2006; 119: 21–31.

5. Hyatt RE: The interrelationships of pressure, flow, and volume during various respiratory maneuvers in normal and emphysematous subjects. Am Rev Respir Dis 1961; 83: 676–683.

6. Mead J, Turner JM, Macklem PT, Little JB: Significance of the relationship between lung recoil and maximum expiratory flow. J Appl Physiol 1967; 22: 95–108.

7. Eltayara L, Becklake MR, Volta CA, Milic Emili J: Relationship between chronic dyspnea and expiratory flow limitation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1996; 154: 1726–1734.

8. Casanova C, Cote C, de Torres JP, et al.: Inspiratory-to-total lung capacity ratio predicts mortality in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2005; 171: 591–597.

9. Tantucci C: Expiratory flow limitation definition, mechanisms, methods, and significance. Pulm Med 2013; 2013: 749860.

10. Stubbing DG, Pengelly LD, Morse JL, Jones NL: Pulmonary mechanics during exercise in subjects with chronic airflow obstruction. J Appl Physiol Respir Environ Exerc Physiol 1980; 49: 511–515.

11. O'Donnell DE: Ventilatory limitations in chronic obstructive pulmonary disease. Med Sci Sports Exerc 2001; 33:S647–S655.

12. O'Donnell DE, Webb KA: Exertional breathlessness in patients with chronic airflow limitation. The role of lung hyperinflation. Am Rev Respir Dis 1993; 148: 1351–1357.

13. Calligaro GL, Raine RI, Bateman ME, et al.: Comparing dynamic hyperinflation and associated dyspnea induced by metronome-paced tachypnea versus incremental exercise. COPD 2014; 11: 105–112.

14. Weigt SS, Abrazado M, Kleerup EC, et al.: Time course and degree of hyperinflation with metronome-paced tachypnea in COPD patients. COPD 2008; 5: 298–304.

15. Fujimoto K, Yoshiike F, Yasuo M, et al.: Effects of bronchodilators on dynamic hyperinflation following hyperventilation in patients with COPD. Respirology 2007; 12: 93–99.

16. Miller MR, Crapo R, Hankinson J, et al.; ATS/ERS Task Force: General considerations for lung function testing. EurRespir J 2005; 26: 153–161.

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

18. Stocks J, Quanjer PH: Reference values for residual volume, functional residual capacity and total lung capacity. ATS Workshop on Lung Volume Measurements. Official Statement of The European Respiratory Society. Eur Respir J 1995; 8: 492–506.

19. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002; 166: 111–117.

20. Jones PW, Quirk FH, Baveystock CM, Littlejohns P: A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. Am Rev Respir Dis 1992; 145: 1321–1327.

21. Jones PW: St. George's Respiratory Questionnaire: MCID. COPD 2005; 2: 75–79.

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

23. Yan S, Kaminski D, Sliwinski P: Reliability of inspiratory capacity for estimating end-expiratory lung volume changes during exercise in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1997; 156: 55–59.

24. Cooper CB, Calligaro GL, Quinn MM, et al.: Determinants of dynamic hyperinflation during metronome-paced tachypnea in COPD and normal subjects. Respir Physiol Neurobiol 2014; 190: 76–80.

25. Hannink J, Lahaije A, Bischoff E, et al.: Dynamic hyperinflation after metronomepaced hyperventilation in COPD – a 2 year follow-up. Respir Med 2010; 104: 1700–1705.

26. Lahaije A, van Helvoort H, Dekhuijzen R, Heijdra Y: Can COPD patients who hyperinflate during daily life activities be identified by laboratory tests? Respiration 2013; 86: 237–242.

27. Johnson BD, Reddan WG, Pegelow DF, et al.: Flow limitation and regulation of functional residual capacity during exercise in a physically active aging population. Am Rev Respir Dis 1991; 143: 960–967.

28. Guenette JA, Webb KA, O'Donnell DE: Does dynamic hyperinflation contribute to dyspnea during exercise in patients with COPD? Eur Respir J 2012; 40: 322–329.

29. 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.

30. Lahaije AJ, Willems LM, van Hees HW, et al.: Diagnostic accuracy of metronomepaced tachypnea to detect dynamic hyperinflation. Clin Physiol Funct Imaging 2013; 33:62–69.

CHAPTER

5

Endobronchial valves for emphysema without interlobar collateral ventilation (The Stelvio trial)

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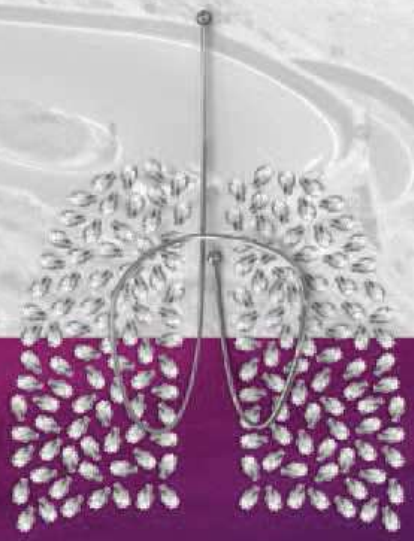


Adapted from

New England Journal of Medicine 2015;373:2325-35.

ABSTRACT

Background

Bronchoscopic lung volume reduction with the use of one-way endobronchial valves is a potential treatment for patients with severe emphysema. To date, the benefits have been modest but have been hypothesized to be much larger in patients without interlobar collateral ventilation than in those with collateral ventilation.

Methods

We randomly assigned patients with severe emphysema and a confirmed absence of collateral ventilation to bronchoscopic endobronchial valve treatment (EBV group) or to continued standard medical care (control group). Primary outcomes were changes from baseline to 6 months in forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and distance on 6 minute walk test.

Results

Eighty-four patients were recruited, of whom 16 were excluded because they had collateral ventilation (13 patients) or because lobar segments were inaccessible to the endobronchial valves (3 patients). The remaining 68 patients (mean age, 59±9 years; 46 were women) were randomly assigned to the EBV group (34 patients) or the control group (34 patients). At baseline, the FEV_1 and FVC were 29±7% and 77±18% of the predicted values, respectively, and the distance on 6 minute walk test was 374±86 meter.

Intention-to-treat analyses showed significantly greater improvements in the EBV group than in the control group from baseline to 6 months: the increase in FEV_1 was greater in the EBV group than in the control group by 140 ml (95% confidence interval [CI], 55 to 225), the increase in FVC was greater by 347 ml (95% CI, 107 to 588), and the increase in the distance on 6 minute walk test was greater by 74 meter (95% CI, 47 to 100) ($P<0.01$ for all comparisons).

By 6 months, 23 serious adverse events had been reported in the EBV group, as compared with 5 in the control group ($P<0.001$). One patient in the EBV group died. Serious treatment related adverse events in this group included pneumothorax (18% of patients) and events requiring valve replacement (12% of patients) or removal (15% of patients).

Conclusion

Endobronchial valve treatment significantly improved pulmonary function and exercise capacity in patients with severe emphysema characterized by an absence of interlobar collateral ventilation.

INTRODUCTION

Bronchoscopic lung volume reduction with the use of one-way endobronchial valves has emerged as a potential treatment for patients with severe emphysema. This treatment was previously investigated in the randomized, controlled Endobronchial Valve for Emphysema Palliation Trial (VENT),[1] which showed significant but moderate improvements in forced expiratory volume in 1 second (FEV_1): an increase from baseline of 4.3% (95% confidence interval [CI], 1.4 to 7.2). Post-hoc analyses of the VENT data suggested that endobronchial valve treatment might be more effective in patients who had a complete fissure (as compared with an incomplete fissure) between the lobe that was targeted for treatment and the adjacent lobe on high-resolution computed tomography scan and when endobronchial valve treatment resulted in complete occlusion of the target lobe.[1] A complete fissure on CT scan is a surrogate finding for the absence of interlobar collateral ventilation; if there is collateral ventilation, an occluded lobe can be reinflated through its collaterals.[2] It is difficult to assess the completeness of the fissure on CT scan in order to predict the absence of collateral ventilation, with considerable interobserver variation.[3] Temporary bronchoscopic lobar occlusion, achieved by inflation of a balloon catheter in the lobar bronchus, is another way to assess collateral ventilation. When combined with CT scan, this method has been shown to increase the predictability of lung volume reduction after endobronchial valve treatment.[4] We conducted a randomized, controlled study, called STELVIO, to examine the effectiveness of endobronchial valve treatment in patients with severe emphysema in whom the absence of collateral ventilation had been proved.

METHODS

Study Design and Oversight

This was a randomized, controlled study comparing endobronchial valve treatment with standard medical care,[5] with crossover at 6 months to endobronchial valve treatment for patients assigned to standard medical care. The study was performed, in accordance with the provisions of the Declaration of Helsinki, at the University Medical Center Groningen (UMCG), in the Netherlands, and was approved by the UMCG ethics committee. All patients gave written informed consent. All devices were obtained commercially from Pulmonx Corporation, Redwood Vity, CA, USA (all catheters at regular market prices and all valves at 50% of the market list price); Pulmonx was not involved in any part of the study.

Patients

Patients with emphysema who were older than 35 years of age and had stopped smoking more than 6 months earlier were eligible for the study if they had a post-bronchodilator FEV_1 that was less than 60% of the predicted value, total lung capacity that was more than 100% of the predicted value, and residual volume that was more than 150% of the predicted value, with a score on the modified Medical Research Council (mMRC) scale[6] of more than 1. An additional criterion for eligibility was a lobe that was determined to be a target for treatment, with a complete or nearly complete fissure between the target lobe and the adjacent lobe as visually judged on CT scan.

The main exclusion criteria were evidence of collateral ventilation in the target lobe and failure to achieve lobar occlusion with endobronchial valves, as noted below.

Randomization

We randomly assigned patients in a 1:1 ratio to receive endobronchial valve treatment (EBV group) or standard care (control group), using a randomization list that was computer generated in blocks of four. The principal investigator and study personnel did not have access to the list. The generated codes were placed in opaque sealed envelopes, which were numbered sequentially. After completion of baseline measurements (pulmonary function tests, 6 minute walk test, and questionnaires) and when study criteria apart from bronchoscopy had been met, the assigned envelope was opened before bronchoscopy in the presence of the patient and bronchoscopist. Bronchoscopy was then performed, and patients with collateral ventilation or airways unsuitable for endobronchial valve placement were excluded. When a patient was excluded, the treatment assignment was placed in a newly sealed envelope and inserted back into the randomization sequence.

Procedures

Collateral ventilation was assessed by means of the Chartis system (Pulmonx Corporation) as previously described.[4] Briefly, during bronchoscopy (performed with a flexible bronchoscope [Olympus BF-1TQ180] with a 2.8 mm working channel) while the patient was under conscious sedation (with the administration of propofol and remifentanil), the target lobar airway was temporarily occluded by means of a balloon catheter, which blocks inspiratory flow but allows expiratory flow. A continuous expiratory flow through the catheter indicates collateral ventilation, and a flow gradually declining to zero indicates no collateral ventilation. Zephyr endobronchial valves (Pulmonx Corporation) were placed in all segments or subsegments of the target lobe as previously described, with the patient under either general anesthesia or conscious sedation.[1,4] Valve placement was performed during the initial bronchoscopic procedure for patients assigned to the EBV group and at 6 months for patients assigned to the control group.

Outcome Measures

Primary outcome measures were improvements from baseline to 6 months in FEV_1, forced vital capacity, and distance on 6 minute walk test in the EBV group as compared with the control group. Secondary outcome measures, among patients who completed the study, were improvements from baseline to 6 months in FEV_1, forced vital capacity, distance on 6 minute walk test, the total score on the St. George's Respiratory Questionnaire (SGRQ),[7,8] the score on the Clinical COPD (chronic obstructive pulmonary disease) Questionnaire (CCQ),[9] and the total volume of the treated lobe on inspiratory CT scan. Clinical response was defined on the basis of established minimal clinically important differences from baseline (FEV_1, a 10% increase[10]; distance on 6 minute walk test, a 26 meter increase[11]; SGRQ score, a 4 point reduction[8]; CCQ score, a 0.4 point reduction[9]; total volume of the treated lobe, a 350 ml reduction on CT scan[2]; and residual volume, a 430 ml reduction[12]). Safety data were collected during the study.

At baseline, at 1 month and 6 months of follow-up, the 6 minute walk test was performed according to ATS recommendations,[13] and the SGRQ,[7] CCQ,[9] and mMRC[6] scores were obtained. Spirometry, whole body plethysmography, and carbon monoxide diffusing capacity (measured with the Jaeger MasterScreen, CareFusion) were performed according to ATS/ERS guidelines[14,15] by assessors who were unaware of the study-group assignments. HRCT scan was performed at baseline and at 6 months after endobronchial valve treatment. Target lobe selection and fissure integrity were assessed visually on the baseline inspiratory HRCT scan (SOMATOM Sensation 64 eco, Siemens Healthcare; slice thickness, 1.0 mm) with the use of the AquariusNET viewer V4.4.7.85 (TeraRecon). After study completion, computerized quantifications were performed on the HRCT data set (Thirona Lung Quantification, version 15.01).[16,17] We calculated lobar volumes and the percentage of voxels of less than −950 Hounsfield units (an indicator of the fraction of emphysematous lung). We classified the distribution of emphysema in the treated lung as homogeneous if the destruction scores for the upper and lower lobes differed by less than 15% and as heterogeneous if the scores differed by 15% or more.

Statistical Analysis

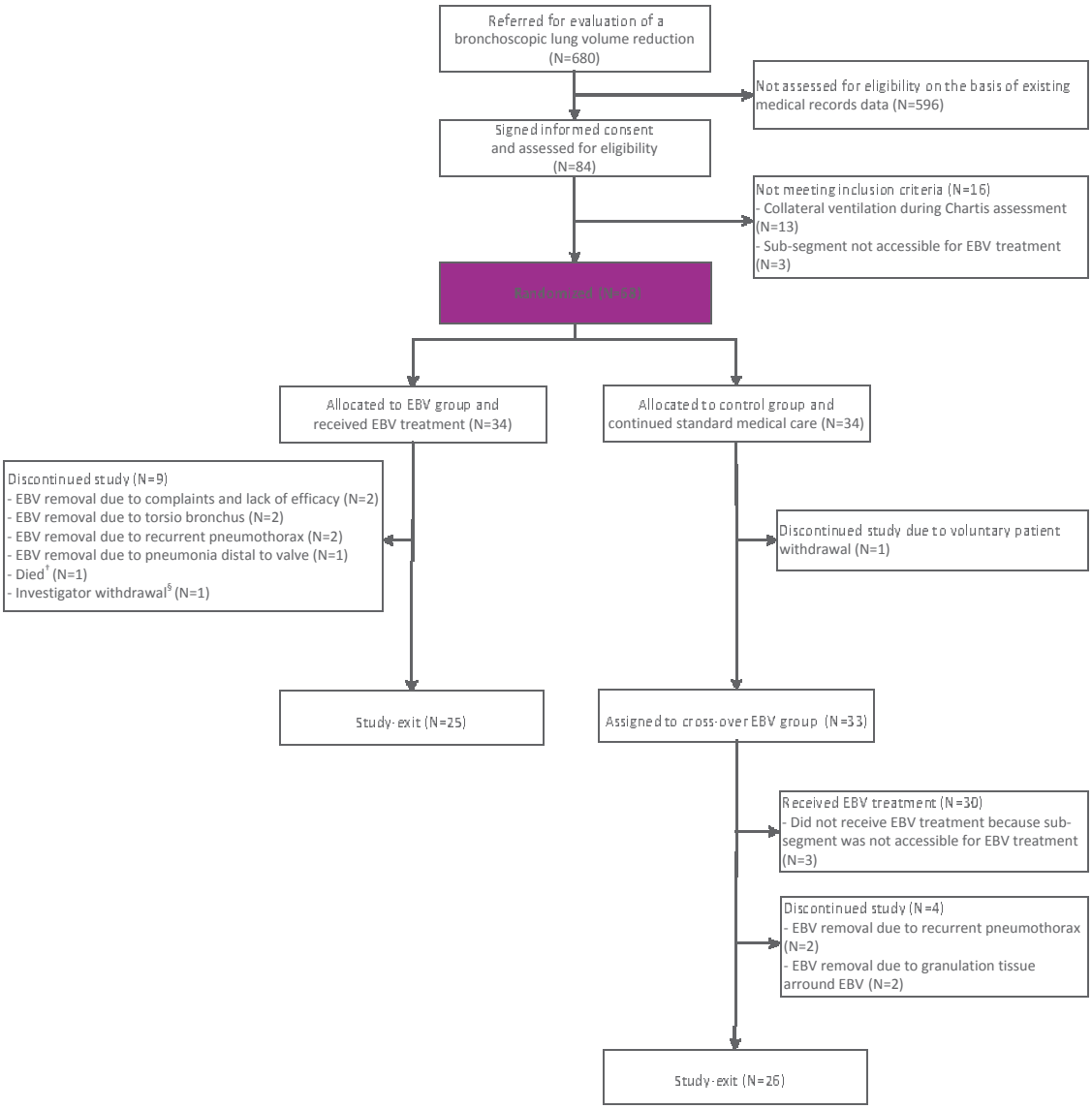
The initial sample size was based on the available post-hoc analyses of the active treatment groups in the VENT, international VENT, and Chartis trial[1,2,4] and on our preliminary findings. With an alpha level at 5% and a beta level at 20%, we calculated that we would need to randomly assign 28 patients to the study groups (14 per group), all of whom could be fully evaluated with respect to the change in the percentage of the predicted FEV_1. A subsequent interim analysis for safety, withdrawal from the study, and assessment of the accuracy of FEV_1 assumptions showed a higher pneumothorax rate and a lower mean difference from baseline for the percentage of the predicted FEV_1 than we had assumed. To account for these findings, 68 patients were deemed necessary for randomization. A two-sample t-test and Fisher's exact test were performed to test for differences between groups at baseline. Intention-to-treat analyses were performed on the primary end points; if there were no available data after study exit, then multiple imputation was used for missing data. Primary, secondary, and other efficacy outcomes were also evaluated in analyses restricted to patients who completed the study. Paired t-tests were used, or in the absence of a normal distribution, the Wilcoxon signed-rank test was used, to compare the groups with respect to changes from baseline to 6 months in study outcomes. Bonferroni correction was performed for multiple comparisons for the three primary end points. P values of less than 0.0167, for primary outcomes, and less than 0.05, for secondary outcomes, were considered to indicate statistical significance. For each outcome, response rates were calculated by counting the number of patients who had a change from baseline that met the criterion for a minimal clinically important difference. Fisher's exact test was performed for calculations of between-group differences in outcomes and adverse events. SPSS Statistics, version 22 (IBM), was used for all analyses. For detailed information about study methods, including the statistical analysis, see the Supplementary Appendix and the full text of this article at NEJM.org.

RESULTS

Study Patients

The study was conducted between June 2011 and November 2014. Eighty-four patients were screened and underwent baseline bronchoscopy. Of these patients, 16 were excluded because they had collateral ventilation (13 patients) or because the airway anatomy was not suitable for endobronchial valve placement (3 patients), resulting in a total of 68 patients who underwent randomization (figure 1, consort diagram).

Figure 1. Consort diagram.



EBV denotes endobronchial valve. † One subject died 58 days post endobronchial valve treatment due to end stage COPD with respiratory failure. § Investigator withdrawal; patient could not perform the 6 month follow-up visit due to a long intensive care unit admission with 2 weeks of invasive ventilation due to a COPD exacerbation caused by a documented viral infection.

A total of 9 patients in the EBV group and 1 in the control group were not able to complete 6 months of follow-up. Among the patients in the control group who crossed over to endobronchial valve treatment at 6 months, lobar occlusion was not possible in 3 patients because the airway anatomy was not suitable for endobronchial valve placement, and this had not been detected during baseline bronchoscopy. Baseline characteristics were similar in the two study groups except that there were more women in the control group than in the EBV group (28 versus 18, P=0.01) (table 1; values are means ± standard deviation).

Table 1. Baseline characteristics of the patients.

Characteristic	EBV group (N=34)	Control group (N=34)
Female sex — no. (%)	18 (53)	28 (82)
Age — years	58±10	59±8
Body-mass index	24.1±3.5	24.2±4.0
Cigarette smoking — no. of pack-years	37±18	35±19
FEV_1 — Liter	0.86±0.30	0.79±0.27
FEV_1 — % of predicted value	29±7	29±8
FVC — Liter	2.80±0.83	2.50±0.90
FVC — % of predicted value	78±16	77±20
RV — Liter	4.64±1.31	4.43±0.72
RV — % of predicted value	216±36	220±32
TLC — Liter	7.85±1.54	7.31±1.20
TLC — % of predicted value	130±13	133±10
Ratio of RV to TLC — %	59±9	61±8
DL_{CO} — ml/min/mmHg	10.4±3.2	9.8±2.5
DL_{CO} — % of predicted value	38.7±9.1	39.0±9.7
PaO_2 (breathing ambient air) — mmHg	69±12	69±9
$PaCO_2$ (breathing ambient air) — mmHg	38±6	38±4
Distance on 6 minute walk test — meter	372±90	377±84
SGRQ — points	59.1±13.7	59.3±11.6
mMRC — points	2.7±0.8	2.7±0.6
CCQ — points	2.9±0.8	2.7±0.6
Target lobe volume — ml	1993±742	1716±555
Target lobe voxels below -950 Hounsfield units — %	47.7±8.2	45.7±7.3
Homogeneous — no. (%)	18 (53)	18 (53)
Heterogeneous — no. (%)	16 (47)	16 (47)
Alpha-1 deficiency — no. (%)	4 (12)	3 (9)
Previous pneumothorax — no. (%)	2 (6)	1 (3)
Regular physical activity — no. (%)	27 (79)	26 (76)

Procedure

Endobronchial valve treatment was performed in 34 patients in the first component of the study. A median of 4 endobronchial valves (range, 2 to 7) were placed per patient, with a median procedure time of 18 minutes (range, 6 to 51). The median post-treatment hospital stay was 1 day (range, 1 to 13). For a detailed description of the procedure, see table 2 and the Supplementary Appendix.

Table 2. Procedure results endobronchial valve group.

	EBV group (N=34)
Endobronchial valve placement median duration time — min. (range)	18 (6 to 51)
Total endobronchial valves placed — no.	152
size 4.0-LP — no.(%)	6 (3.9)
size 4.0 — no.(%)	56 (36.8)
size 5.5 — no.(%)	90 (59.2)
Endobronchial valves placed per patient — median no. (range)	4 (2 to 7)
Post-endobronchial valve procedure hospital stay — median days (range)	1 (1 to 13)
General anesthesia during endobronchial valve placement — no.(%)	26 (76.5)
Conscious sedation during endobronchial valve placement — no.(%)	8 (23.5)
Target lobe for endobronchial valve treatment	
Right Upper lobe — no.(%)	4 (11.8)
Middle lobe — no.(%)	0
Right Lower lobe — no.(%)	4 (11.8)
Left Upper lobe — no.(%)	11 (32.4)
Left Lower lobe — no.(%)	9 (26.5)
Right Upper + Middle lobe — no.(%)	6 (17.6)

Primary Outcomes

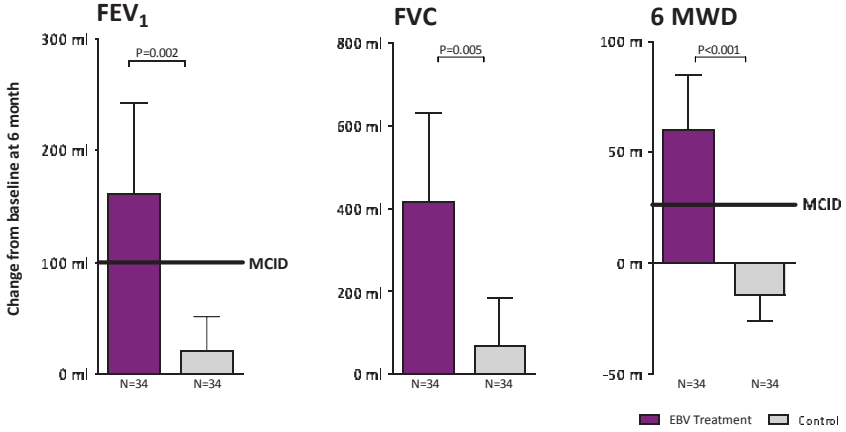
In the intention-to-treat population, changes from baseline to 6 months in FEV_1, FVC, and in distance on the 6 minute walk test were significantly greater in the EBV group than in the control group (P<0.01 for all comparisons) (table 3 and figure 2a).

Table 3. Mean change from baseline to 6 months of follow-up in primary efficacy outcomes in the Intention-to-treat population.

Variable	EBV group (N=34)	Control group (N=34)	Between-Group Difference	P value
Change in FEV_1				
— ml (95% CI)	161 (80 to 242)	21 (-9 to 52)	140 (55 to 225)	0.002
— % (95% CI)	20.9 (11.1 to 30.7)	3.1 (-0.4 to 6.6)	17.8 (7.6 to 28.0)	0.001
MCID reponders	59%	24%	-	0.003
Change in FVC				
— ml (95% CI)	416 (201 to 631)	69 (-50 to 187)	347 (107 to 588)	0.005
— % (95% CI)	18.3 (9.3 to 27.3)	4.0 (-0.7 to 8.6)	14.4 (4.4 to 24.3)	0.005
Change in 6MWD				
— meter (95% CI)	60 (35 to 85)	-14 (-25 to -3)	74 (47 to 100)	<0.001
— % (95% CI)	19.6 (10.4 to 28.9)	-3.6 (-6.9 to -0.4)	23.3 (13.6 to 32.9)	<0.001
MCID responders	59%	6%	-	<0.001

Paired t-tests were used to calculate within-group mean differences in changes from baseline to 6 months, P values, and 95% confidence intervals. Two-sample t-tests or, in the absence of a normal distribution, Wilcoxon signed-rank tests were used to calculate between-group mean differences, P values, and 95% confidence intervals. Fisher's exact test was used to calculate the between-group difference in response rates. Response rates were calculated by counting the number of patients for whom the change at 6 months met or exceeded the minimal clinically important difference for FEV_1 (>10%)[10] and the distance on 6 minute walk test (>26 meter).[11]

Figure 2a. Primary outcomes in the intention-to-treat population.



Shown are primary outcomes in the intention-to-treat population, according to the assigned study group (endobronchial valve group or control group). Horizontal lines represent the minimal clinically important difference (MCID) for the following outcomes: forced expiratory volume in 1 second (FEV_1),[10] an increase of 100 ml; 6 minute walk distance (6MWD),[11] an increase of 26 meter. T bars indicate 95% confidence intervals. FVC denotes forced vital capacity.

Secondary Outcomes

Analyses of data for patients who completed the study (25 patients in the EBV group and 33 in the control group) showed significant improvements in the secondary outcome measures from baseline to 6 months in the EBV group as compared with the control group: the increase in FEV_1 was greater in the EBV group than in the control group by 191 ml (95% CI, 109 to 272), the increase in forced vital capacity was greater by 442 ml (95% CI, 215 to 668), and the increase in the 6 minute walk distance was greater by 106 meter (95% CI, 80 to 133) (P<0.001 for all between-group comparisons); improvements were also seen in SGRQ scores, with a 14.7-point greater reduction in the EBV group than in the control group (95% CI, -21.8 to -7.6; P<0.001), and in CCQ scores, with a 0.74-point greater reduction in the EBV group than in the control group (95% CI, -1.20 to -0.27; P = 0.002).

In the EBV group, the median change from baseline in target lobar volume on HRCT was a reduction of 1366 ml (range, -3604 to -28; P<0.001) (table 4 en figure 2b). Significantly more patients in the EBV group than in the control group had changes from baseline measures that exceeded the established minimal clinically important difference (P<0.001 for all comparisons) (figure 3 and table 5).

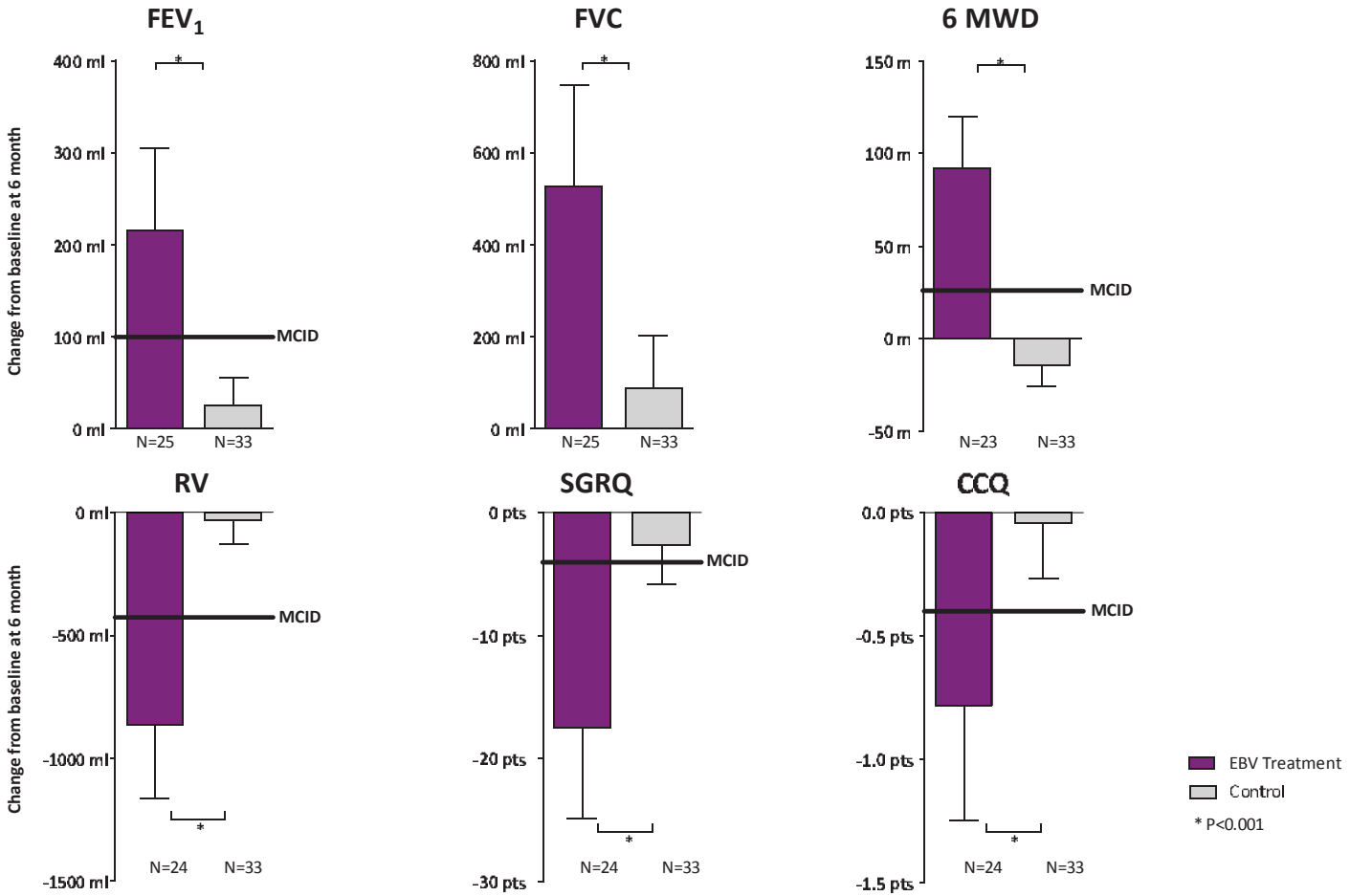
Among patients who completed the study, those who crossed over to endobronchial valve treatment at 6 months had improvements that were very similar to the improvements in the EBV group (table S2 in the Supplementary Appendix). Post-hoc analysis of CT scan findings in patients who completed the study showed that for patients with heterogeneous emphysema and for those with homogeneous emphysema, there was a significant between-group difference in FEV_1, 6 minute walk distance, residual volume, and SGRQ score in favor of the EBV group at 6 months of follow-up. The effects tended to be larger in patients with heterogeneous emphysema than in those with homogeneous emphysema (table S3 in the Supplementary Appendix).

Table 4. Mean change from baseline to 6 months of follow-up in efficacy outcomes among patients who completed the study.

Variable		EBV group	Control group	Difference	P value
Change in FEV_1		N=25	N=33		
	— ml (95% CI)	216 (128 to 304)	26 (-4 to 56)	191 (109 to 272)	<0.001
	— % (95% CI)	26.5 (16.3 to 36.4)	3.6 (0.1 to 7.1)	22.7 (12.2 to 33.3)	<0.001
Change in FVC		N=25	N=33		
	— ml (95% CI)	529 (309 to 748)	87 (-29 to 203)	442 (215 to 668)	<0.001
	— % (95% CI)	22.0 (12.6 to 31.5)	4.6 (-0.0 to 9.2)	17.4 (7.9 to 26.9)	0.001
Change in 6MWD		N=23	N=33		
	— meter (95% CI)	92 (64 to 120)	-14 (-26 to -3)	106 (80 to 133)	<0.001
	— % (95% CI)	30.0 (18.5 to 41.4)	-3.7 (-7.1 to -0.4)	33.7 (21.8 to 45.5)	<0.001
SGRQ Total score		N=24	N=33		
	— points	-17.4 (-24.8 to -10.0)	-2.7 (-5.9 to 0.5)	-14.7 (-21.8 to -7.6)	<0.001
CCQ Total score		N=24	N=33		
	— points	-0.87 (-1.25 to -0.31)	-0.04 (-0.26 to 0.18)	-0.74 (-1.20 to -0.27)	0.002
TLVR on CT scan		N=25			
	— ml	-1366 (-3604 to -28)	-	-	-
Total lung capacity		N=24	N=33		
	— ml	-384 (-512 to -256)	-2 (-68 to 64)	-382 (-512 to -252)	<0.001
Residual volume		N=24	N=33		
	— ml	-865 (-1166 to -563)	-34 (-128 to 61)	-831 (-1101 to -560)	<0.001

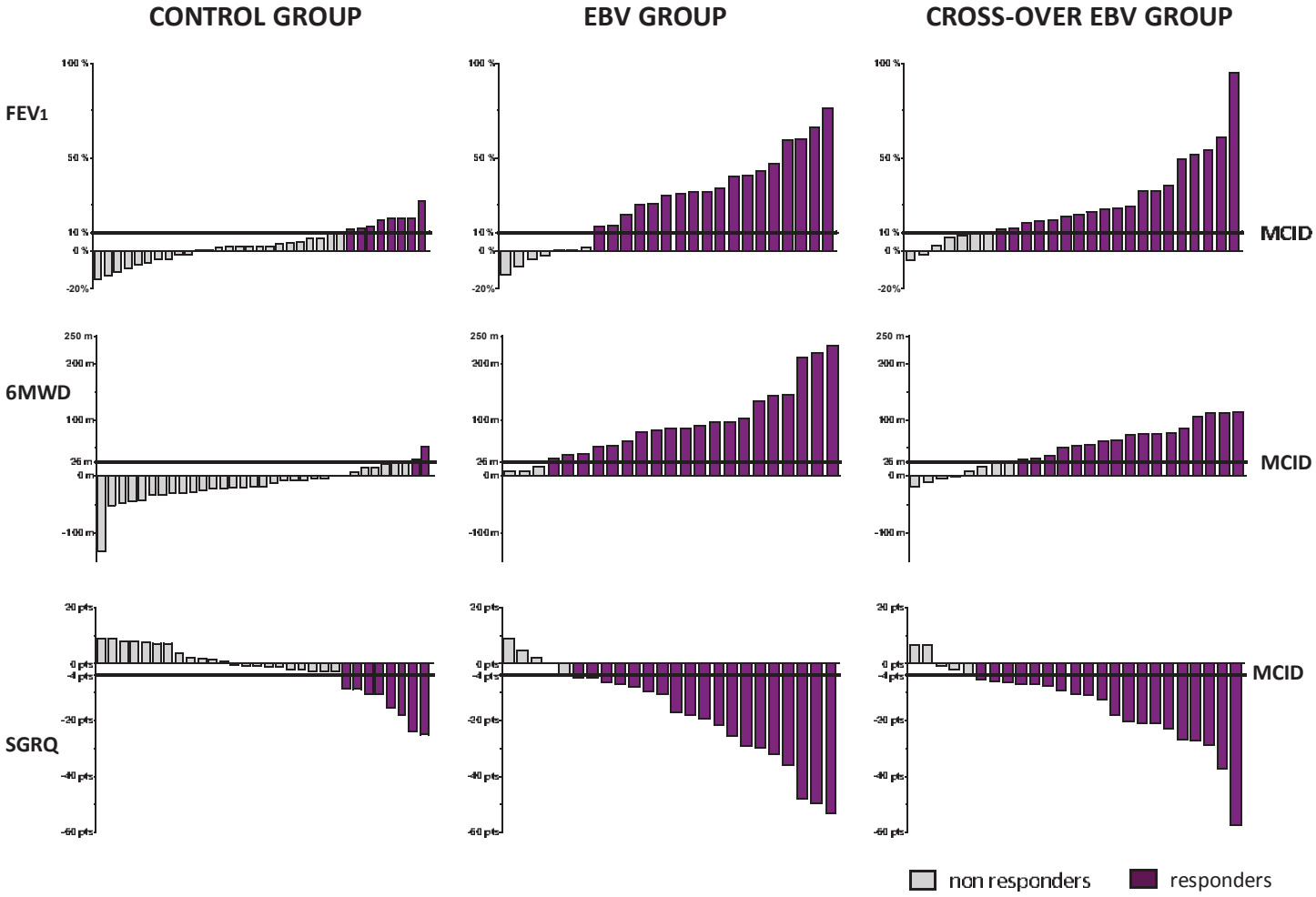
Paired t-tests were used to calculate within-group mean differences in changes from baseline to 6 months, P values, and 95% confidence intervals. Two-sample t-tests or, in the absence of a normal distribution, Wilcoxon signed-rank tests were used to calculate between-group mean differences, P values, and 95% confidence intervals. Fisher's exact test was used to calculate the between-group difference in response rates. Response rates were calculated by counting the number of patients for whom the change at 6 months met or exceeded the minimal clinically important difference for FEV_1 (>10%)[10] and the distance on 6 minute walk test (>26 meter).[11] TLVR denotes target lobar volume reduction.

Figure 2b. Secondary outcomes among the patients who completed the study.



Shown are secondary outcomes among patients who completed the study, according to the assigned study group (endobronchial valve group or control group). Horizontal lines represent the minimal clinically important difference (MCID) for the following outcomes: forced expiratory volume in 1 second (FEV_1),[10] an increase of 100 ml; 6 minute walk distance (6MWD),[11] an increase of 26 meter; SGRQ score,[8] a reduction of 4 points, CCQ score,[9] a reduction of 0.4 points; and residual volume (RV),[12] a reduction of 430 ml. T bars indicate 95% confidence intervals. FVC denotes forced vital capacity.

Figure 3. MCID responder results for control group, endobronchial valve group and Cross-over group among the patients who completed the study.



EBV denotes endobronchial valve. One bar represents a patient. Light-grey colored bars represents the patients who were not reaching the MCID. Pink colored bars represents the patients who did reach the MCID. MCID denotes minimal clinically important difference.

Table 5. Summary of the responder rates among patients who completed the study.

MCID responder rate	Control	EBV	Cross-over EBV
FEV_1 (+10%)	**24%** (N=8 of 33)	**72%** (N=18 of 25)	**73%** (N=19 of 26)
6MWD (+26 meter)	**12%** (N=4 of 33)	**87%** (N=20 of 23)	**68%** (N=17 of 25)
SGRQ (-4 points)	**33%** (N=11 of 33)	**79%** (N=19 of 24)	**80%** (N=20 of 25)
CCQ (-0.4 points)	**30%** (N=10 of 33)	**63%** (N=15 of 24)	**64%** (N=16 of 25)
TLVR on CT scan (-350 ml)	-	**88%** (N=22 of 25)	**96%** (N=25 of 26)
RV (-430 ml)	**3%** (N=1 of 33)	**71%** (N=17 of 24)	**64%** (N=16 of 25)
RV/TLC (-4%)	**9%** (N=3 of 33)	**63%** (N=15 of 24)	**60%** (N=15 of 25)

Response rates were calculated by counting the number of patients for whom the change at 6 months met or exceeded the minimal clinically important difference. TLVR: target lobar volume reduction, RV: residual volume, TLC: total lung capacity, 6MWD: distance on 6 minute walk test.

Adverse Events

One pneumothorax was detected in 84 assessments that were performed by means of the Chartis system. In 7 of the 34 patients in the EBV group (21%), the endobronchial valves were associated with unacceptable adverse events and had to be removed. There were 23 serious adverse events in the EBV group, as compared with 5 in the control group (P<0.001) (Table 6). In the EBV group, treatment-related serious adverse events included pneumothorax (in 18% of patients), other events requiring valve replacement (in 12% of patients) or valve removal (in 15% of patients), and 1 death due to end-stage COPD with respiratory failure 58 days after treatment. All adverse events are listed in tables S4 and S5 in the Supplementary Appendix.

Pneumothorax

In the EBV group, the frequency of pneumothorax was 18% (6 of 34 patients). In 1 patient, the pneumothorax resolved spontaneously; in 5 patients, insertion of a chest tube was required, with temporary removal of endobronchial valves in 1 patient to promote pneumothorax healing and permanent removal of all valves in 2 patients because of recurrent pneumothorax, after which resolution occurred. No surgical procedures were used to control the pneumothorax.

Repeat Bronchoscopy

Bronchoscopy was repeated in 12 of 34 patients in the EBV group (35%). Reasons for repeat bronchoscopy were permanent removal of endobronchial valves because of recurrent pneumothorax (in 2 patients), torsion of the left lower lobe bronchus after left upper lobe treatment (in 2 patients), pneumonia distal to the valves (in 1 patient), and markedly increased dyspnea and sputum production without a treatment benefit, as perceived by the patient (in 2 patients); and temporary removal of endobronchial valves to promote healing of a pneumothorax, with valve replacement after 2 months (in 1 patient). Other reasons for repeat bronchoscopy were valve replacement due to migration (in 2 patients), valve dislocation because of granulation-tissue formation (in 1 patient), and persistent cough, with valve replacement in the other lobe (in 1 patient). (For additional information, see Supplementary Appendix.)

Table 6. Serious adverse events during 6 months of follow-up.

Event	EBV group (N=34) no. (%)	Control group (N=34) no. (%)	P Value
Total number of serious events	**23**	**5**	**<0.001**
Pulmonary event			
Death[§]	1 (3)	0 (0)	1.00
COPD exacerbation with hospitalization	4 (12)	2 (6)	0.67
Pneumonia	2 (6)	1 (3)	1.00
Pneumothorax	**6 (18)**	**0**	**0.02**
Resolved ≤ 14 days after onset, without drainage	1 (3)	0	1.00
Resolved ≤ 14 days after onset, with drainage	2 (6)	0	0.49
Required temporary valve removal[≠]	1 (3)	NA	NA
Required permanent valve removal because of recurrent pneumothorax	1 (3)	NA	NA
Required permanent valve removal, after temporary removal and reimplantation, because of recurrent pneumothorax	1 (3)	NA	NA
Other endobronchial valve related events requiring permanent removal of all valves			
Torsion of the bronchus	2 (6)	NA	NA
Pneumonia distal to valve	1 (3)	NA	NA
Increased sputum, dyspnea, or coughing without patient-perceived treatment benefit	2 (6)	NA	NA
Other endobronchial valve related events requiring valve replacement			
Valve migration	2 (6)	NA	NA
Valve expectoration	0	NA	NA
Valve dislocation due to formation of granulation tissue	1 (3)	NA	NA
Increased sputum, dyspnea, or coughing	1 (3)	NA	NA
Non-Pulmonary event			
Stroke	1 (3)	2 (6)	1.00

Serious adverse events were all adverse events that were fatal, required or prolonged hospitalization, caused substantial risk of death at the time of the event, resulted in permanent impairment of a body function, or required medical or surgical intervention to prevent permanent impairment of a body function. Non serious adverse events during 6 months of follow-up are listed in table S5 in the Supplementary Appendix. NA denotes not applicable. A two-sided Fisher's exact test was used to calculate the difference in adverse events between the EBV group and the control group. [§]The patient died from end-stage chronic obstructive pulmonary disease with respiratory failure 58 days after endobronchial valve treatment.

DISCUSSION

We found that endobronchial valve treatment in patients with emphysema and a proven absence of interlobar collateral ventilation provided a measurable clinical benefit, with significantly improved lung function, exercise capacity, and quality of life, as compared with usual care. The reduction in lung volume with subsequent positive outcomes was accompanied by adverse effects, mainly pneumothorax, which was managed by means of regular care (including chest-tube drainage) but sometimes required repeated bronchoscopy. The endobronchial valves were retained throughout the 6 month study period in 79% of the initially treated patients.

This prospective, randomized, controlled trial confirmed the results of open-label and post-hoc studies assessing responses to endobronchial valve treatment.[1,2,4,18] In the VENT,[1] the overall benefits were moderate, but post-hoc analysis showed a significantly greater improvement in FEV_1 in patients with a complete fissure, which indicates an absence of collateral ventilation, than in those with an incomplete fissure. A previous multicenter study validating the Chartis system, which measures collateral ventilation, showed that treatment success was not associated with the method of fissure assessment (i.e., fissure assessment by means of highly dedicated HRCT versus assessment by means of the Chartis system).[4] However, the current results show that when collateral ventilation is assessed, the overall outcome of treatment is positive. In our study, 84 patients were preselected on the basis of having complete or nearly complete fissures on HRCT scans, with an additional 13 of those patients (15%) excluded on the basis of assessment by means of the Chartis system. We think it is reasonable to speculate that these patients with collateral ventilation would not have had a benefit from endobronchial valve treatment.

Among the patients who completed the study, there was a significant benefit of the treatment on FEV_1, residual volume, 6 minute walk distance, and scores on the CCQ and SGRQ, with effect sizes all well above the established minimal clinically important differences for these variables (figure 2b). The improvements with endobronchial valve treatment tended to be larger in patients with emphysema that was heterogeneous than in those with emphysema that was homogeneous, although we observed improvements in both subgroups, a finding that was also suggested by post-hoc analysis of the data from the international VENT.[2] Although comparisons among studies is difficult, it is interesting to note that the improvements we found were of greater magnitude than those noted with pharmacologic treatment in comparable patients and were similar to improvements with surgical lung volume reduction, but with significantly less morbidity.[19,20]

Even though the trial was randomized and controlled, the large improvements in SGRQ scores could have been influenced by the open label design. A previous trial of bronchoscopic intervention, in which a sham control was used, showed that placebo effects were limited in patients with severe COPD.[21] Two other sources of potential bias should be considered: both patients and bronchoscopists were aware of the treatment assignment at the time of bronchoscopy, and the revealed treatment assignments for the patients with collateral ventilation or unsuitable airways for endobronchial valve placement were put back in the

randomization sequence in newly sealed envelopes. However, baseline characteristics were similar in the two study groups, except for sex distribution. In addition, the results for the patients in the control group who crossed over to endobronchial valve treatment at 6 months were similar to those for the original EBV group.

Pneumothorax, which was the most frequent adverse event, is thought to be due to a rapid shift in lung volumes caused by the rupture of blebs or bullae, the rupture of parenchyma due to pleural adhesions, or the response to barotrauma.[22] The observed frequency of pneumothorax (18%) in our study was higher than the frequencies reported in earlier trials (VENT in 2010, 4%[1]; Chartis trial in 2013, 8%[4]) but was similar to the frequency in an analysis of German data from 2014 (23%[23]). This increase in the frequency of pneumothorax is probably the result of more successful execution of endobronchial valve treatment (resulting in a higher percentage of patients having a significant reduction in lobar volume) and patient selection (i.e., patients without collateral flow). All cases of pneumothorax in the EBV group occurred within 1 day after endobronchial valve treatment, when the patients were still hospitalized. Because a pneumothorax is a potentially life-threatening complication in patients with severe emphysema, we found that close monitoring of patients after endobronchial valve treatment, including monitoring after discharge, was crucial. All cases of pneumothorax in our study were managed according to published guidelines.[22,24]

Repeat bronchoscopy is sometimes necessary to replace or temporarily or permanently remove endobronchial valves. Reasons to do so include loss of initial lung volume reduction due to formation of granulation tissue or valve migration. Previous studies postulated that endobronchial valve treatment is fully reversible and does not preclude future therapeutic options.[1,2,4] Our study provides confirmation of this view, since all patients in whom endobronchial valves were removed recovered without further side effects.

CONCLUSION

We found that in patients with severe emphysema who were preselected on the basis of a proven absence of interlobar collateral ventilation, endobronchial valve treatment improved pulmonary function, exercise capacity, and quality of life, even when we considered patients in whom valve removal was required. Adverse events, including potentially life-threatening events, occurred and required careful follow-up.

The picture of the Stelvio Pass is made by Dirk-Jan Slebos.

Background information about the name of the trial: "The STELVIO"

The patients in our trial are severe COPD patients, and for them it is every day a big "challenge" when they take a shower, walking stairs, doing groceries etc., you can compare it with climbing a mountain every day. It was difficult to find an acronym for the study "Endobronchial Valves for Emphysema without Interlobar Collateral Ventilation", and we also would like to have an "easy and short" name like "NETT" or "VENT". Therefore, we choose to call our trial after the most challenging mountain pass of the Alps (this is a legend in the world of cycling). The Stelvio Pass is a mountain pass in northern Italy, at an elevation of 2757 meter above sea level. It is the highest paved mountain pass in the Eastern Alps There are 3 routes to climb the Stelvio Pass, the climb from Prato is the hardest and most challenging with its famous 48 hairpins and a length of 24.3 kilometer with an average grade of 8%, total elevation is 1817 meter (source Wikipedia). On July 20th 2015, Dirk-Jan and myself have cycled this beautiful mountain pass on our racingbike.

Acknowledgments

We thank Ruth Hiltermann for performing the 6 minute walk tests and obtaining questionnaires; Alie Smidt for support during all bronchoscopies; Marga Star, Yvonne Valkema, Margrietha Swierenga, Jan Bouwman, and Maria Heuving for pulmonary function testing; Martijn Farenhorst for technical support; Wim Tukker from the department of radiology for technical management; Gea Zwart for scheduling the study visits; Laurens Hogeweg for analyzing the CT scans; Judith Vonk for statistical advice; all our anesthesiologists for their work during the bronchoscopies; and the nurses and pulmonary staff.

REFERENCES

1. Sciurba FC, Ernst A, Herth FJ, et al. A randomized study of endobronchial valves for advanced emphysema. N Engl J Med 2010; 363: 1233-44.

2. Herth FJ, Noppen M, Valipour A, et al. Efficacy predictors of lung volume reduction with Zephyr valves in a European cohort. Eur Respir J 2012; 39: 1334-42.

3. Koenigkam-Santos M, Puderbach M, Gompelmann D, et al. Incomplete fissures in severe emphysematous patients evaluated with MDCT: incidence and interobserver agreement among radiologists and pneumologists. Eur J Radiol 2012; 81: 4161-6.

4. Herth FJ, Eberhardt R, Gompelmann D, et al. Radiological and clinical outcomes of using Chartis to plan endobronchial valve treatment. Eur Respir J 2013; 41: 302-8.

5. Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary.
Am J Respir Crit Care Med 2007; 176: 532-5.

6. 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: 581-6.

7. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation: the St. George's Respiratory Questionnaire. Am Rev Respir Dis 1992; 145: 1321-7.

8. Jones PW. St. George's Respiratory Questionnaire: MCID. COPD 2005; 2: 75-9.

9. Kocks JW, Tuinenga MG, Uil SM, et al. Health status measurement in COPD: the minimal clinically important difference of the clinical COPD questionnaire. Respir Res 2006; 7: 62.

10. Donohue JF. Minimal clinically important differences in COPD lung function. COPD 2005; 2: 111-24.

11. Puhan MA, Chandra D, Mosenifar Z, et al. The minimal important difference of exercise tests in severe COPD. Eur Respir J 2011; 37: 784-90.

12. Hartman JE, Ten Hacken NH, Klooster K, et al. The minimal important difference for residual volume in patients with severe emphysema. Eur Respir J 2012; 40: 1137-41.

13. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002; 166: 111-7.

14. Miller MR, Crapo R, Hankinson J, et al. General considerations for lung function testing.
Eur Respir J 2005; 26: 153-61.

15. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J 2005; 26: 319-38.

16. van Rikxoort EM, de Hoop B, Viergever MA, et al. Automatic lung segmentation from thoracic computed tomography scans using a hybrid approach with error detection. Med Phys 2009; 36: 2934-47.

17. van Rikxoort EM, Prokop M, de Hoop B, Viergever MA, Pluim JP, van Ginneken B. Automatic segmentation of pulmonary lobes robust against incomplete fissures. IEEE Trans Med Imaging 2010; 29: 1286-96.

18. Toma TP, Hopkinson NS, Hillier J, et al. Bronchoscopic volume reduction with valve implants in patients with severe emphysema. Lancet 2003; 361: 931-3.

19. Fishman A, Martinez F, Naunheim K, et al. A randomized trial comparing lung volume reduction surgery with medical therapy for severe emphysema. N Engl J Med 2003; 348: 2059-73.

20. Criner GJ, Cordova F, Sternberg AL, Martinez FJ. The National Emphysema Treatment Trial (NETT) Part II: lessons learned about lung volume reduction surgery. Am J Respir Crit Care Med 2011; 184:881-93.

21. Shah PL, Slebos DJ, Cardoso PF, et al. Bronchoscopic lung-volume reduction with Exhale airway stents for emphysema (EASE trial): randomized, sham-controlled, multicentre trial. Lancet 2011; 378: 997-1005.

22. Valipour A, Slebos DJ, de Oliveira HG, et al. Expert statement: pneumothorax associated with endoscopic valve therapy for emphysema — potential mechanisms, treatment algorithm, and case examples. Respiration 2014; 87: 513-21.

23. Gompelmann D, Eberhardt R, Herth F, et al. Endoscopic volume reduction in COPD: a critical review. Dtsch Arztebl Int 2014; 111: 827-33.

24. Gompelmann D, Herth FJ, Slebos DJ, et al. Pneumothorax following endobronchial valve therapy and its impact on clinical outcomes in severe emphysema. Respiration 2014; 87: 485-91.

Supplementary Appendix

'Endobronchial valves for emphysema without interlobar collateral ventilation'

Trial Justification

This trial has been designed to serve the needs of our patients with severe emphysema, understanding that endobronchial valve therapy using best responder criteria has a potential as a treatment for these patients. The trial has not been designed as an industry invoked 'Investigational Device Exemption' trial, but resembles routine daily clinical care for this patient group. This trial 'Endobronchial valves for emphysema without interlobar collateral ventilation' is a 100% investigator initiated and driven trial. The trial, called 'The STELVIO', has been financially supported by a grant (no. 171101008, to University Medical Center Groningen)from The Netherlands (government) Organization for Health Research and Development ZonMw, The Hague, the Netherlands, and innovation funding by the University Medical Center Groningen, the Netherlands. All devices used in the trial have been commercially acquired at 50% price of regular market list price from Pulmonx Corporation, Redwood City, CA, USA. Pulmonx was not involved in any part of the study.

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)

Methods

Patient recruitment

In this study 680 patients were recruited from referrals from pulmonologists all over the Netherlands. Our team evaluated the already existing thoracic computed tomography scan (CT scan), available pulmonary function test reports, medication use, and medical history of each individual referred patient. This data was used as a "pre-screening" for potential study-eligibility. Potential eligible patients were invited for an information visit and provided with the STELVIO trial patient information by the pulmonologist. If a patient agreed, informed consent was signed and a screening visit was scheduled. Out of this "pool" of 680 initial general advance COPD patient referrals, there were 68 patients finally eligible for endobronchial valve treatment in our trial. Based on these data approximately 10% of the patients with advanced COPD will potentially qualify for endobronchial valve treatment in the end.

CT scan

At baseline and 6 months post endobronchial valve treatment (endobronchial valve group and Cross-over endobronchial valve group) a high resolution CT scan, 1 mm and 2 mm slices was performed. The patients in the Control group did not perform a 6 month follow-up CT scan. This trial was designed to resemble 'daily practice' as much as possible. For the treatment of severe emphysema patients with valves, based on the current available literature (post-hoc VENT-trial data[1], Chartis trial data[2], and own clinical experience we choose to visually assess the thoracic HRCT-scan (in our weekly MDT meeting in both axial, coronal and sagittal reconstructions using AquariusNet viewer V4.4.7.85; TeraRecon, Foster City, CA, USA) to look for at least one suitable endobronchial valve treatment 'target' lobe: a lobe(s) that can visually be distinguished from the ipsilateral lobe based on a lower tissue density when compared to the ipsilateral lobe: so looking for "visual heterogeneity".

Chartis assessment

Chartis assessment was performed as previously described[3] under conscious sedation with a flexible bronchoscope (Olympus BF180, Hamburg, Germany, 2.8 mm working channel, 6.0 mm outer diameter). Following recovery from conscious sedation, patients were discharged the same day from the hospital or received the endobronchial valve treatment if patient was randomized for the endobronchial valve group.

Study-device

The one-way endobronchial valve (Zephyr® Pulmonx Corporation,Redwood City USA) was used as study device and was delivered with the use of a flexible endobronchial valve delivery catheter (Pulmonx Corporation, Redwood City, CA, USA) during a bronchoscopy. Endobronchial valve size 4.0 LP (low profile) became available in the last 17 months of this study.

Size one-way endobronchial valve	4.0 LP	4.0	5.5

Endobronchial valve procedure

The target treatment lobes consisted one of the following lobe, Left Upper Lobe (LUL), Left Lower Lobe (LLL), Right Upper Lobe (RUL), Right Lower Lobe (RLL), Right Middle Lobe (RML) or RUL + RML. The treatment lobe was intended to be completely occluded with endobronchial valve placement. Achieving lobar occlusion was verified via bronchoscopy immediately after finishing valve placement. In this study, the bronchoscopy was performed either under conscious sedation or under general anesthesia (using a 9.0 mm endo-tracheal flexible tube) with a flexible bronchoscope (Olympus BF180, Hamburg, Germany, 2.8 mm working channel, 6.0 mm outer diameter). Following recovery from anesthesia, patients stayed in the hospital at least one night for observation. Patients received as per our standard interventional bronchoscopy prophylactic regimen a five days course of prednisolone (25 mg once daily), starting 2 days before the procedure and a five days course of azithromycin (250 mg once daily) starting on the procedure day. A routine bronchial wash was sampled during the bronchoscopy in all patients and sent for culture allowing more precise antibiotic treatment in case of infectious complications.

Pulmonary function measurements

At baseline, at 1 month and 6 months post randomization or post crossover, spirometry, body plethysmography and diffusion capacity (Jaeger MasterScreen™, CareFusion, Germany) were performed by blinded assessors according to the ATS/ERS guidelines[4,5] and using cohort reference values (EGKS'93) from the European Community for Coal and Steel workers.[6]

Six minute walk test

At baseline, at 1 month and 6 months post randomization or post crossover, the 6 minute walk test was performed using ATS recommendations.[7] In our protocol it was not described to perform a practice walk test during baseline. However from literature, we know that there is a learning curve in performing a 6 minute walk test. Because approximately 80% our patients followed regular physical activity under professional supervision, they were all used to regularly perform a 6 minute walk test.

Questionnaires

At baseline, at 1 month and 6 months post randomization or post crossover, the following questionnaires were obtained; Saint George's Respiratory Questionnaire (SGRQ), Clinical COPD questionnaire (CCQ), modified Medical Research Council dyspnea index (mMRC), EuroQol 5-D 3L and EQ-VAS score 3L.

Randomization

Patients were 1:1 randomly assigned to one of the two study groups using a block (N=4) randomization computer generated list. The list was not accessible by the principal investigator or study personnel. The generated codes were placed in opaque sealed envelopes which were numbered sequentially. After all baseline testing (pulmonary function, 6 minute walk test and obtaining questionnaires) and when study criteria apart from bronchoscopy were met the assigned envelope was opened before bronchoscopy in the presence of the patient and bronchoscopist. Bronchoscopy was then performed and

patients with collateral ventilation or unsuitable airways for endobronchial valve placement were excluded. When a patient was excluded the treatment assignment was placed in a newly sealed envelope and inserted back into the randomization sequence. The patients were awake during randomization, and fully aware of their randomization assignment and entered the bronchoscopy much more relaxed. This approach was decided upon in an open dialogue with the ethics committee. It is important to note that our approach did not influence the randomization process. First of all, no patient backed off when understanding that the randomization had provided control treatment first, and endobronchial valve treatment 6 months later. Secondly, baseline characteristics were similar between the two treatment groups (except for gender). Finally, the results of the Cross-over group receiving the endobronchial valve 6 months later showed similar efficacy outcomes, and the same minimal clinically important difference responder rates and radiological response on HRCT to endobronchial valve treatment again suggesting no undue selection biases or influences during the randomization process.

Generation of the randomization list
The randomization list was computer generated produced by an independent trained researcher from another department in our hospital, who also produced the actual randomization envelopes. The list was not accessible by the principal investigator or study personnel.

Block-size
A randomization block-size of 4 was used. The study personnel who were involved in patient care were not informed of the block size used in this study. Patient scheduling was performed independent of the trial personnel involved (see also below).

Envelopes
The generated codes were placed in sealed envelopes (opaque secured envelopes, with no possibility to look through the envelope were used), which were numbered sequentially. The envelopes were opened in the same sequence as the patients were scheduled (the scheduling sequence is done 'blinded' by the administrative staff of our endoscopy ward who has no insight in any of our trials), in the presence of the principal investigator, study coordinator and patient. Once used, the randomization paper was dated and signed. If the envelope was used but replaced, because the patient was not allocated to the endobronchial valve group or Control group, the randomization assignment was put back in a new envelope and sealed by the administrative staff and placed back into the randomization binder.

Follow-up
Patients were maintained on standard medical care and patients maintained supervised physiotherapy for their COPD. These programs were unchanged and not intensified before or after randomization. Safety was assessed during the hospital stay, the follow-up visits, by reporting all adverse events that occurred up to 6 months after endobronchial valve treatment in the endobronchial valve group, and in the Control group up to 6 months after receiving the endobronchial valve treatment if the patient was in the Cross-over group. Follow-up data was collected during the follow-up hospital visits, the data was collected from

both hospital notes and worksheets. A chest X-ray was performed before endobronchial valve treatment and after endobronchial valve treatment the same day, 1 day and at 1 month. During baseline, 1 month and 6 month follow-up visit we performed a 6 minute walk test and obtained questionnaires. PFT measurements (spirometry, body plethysmography and diffusion capacity) were performed by blinded assessors. The same testing sequence was used during baseline and the follow-up visits.

Statistical analysis plan

We based our first power calculations on post-hoc analyses of active treatment FEV_1 data of the VENT-trial[8], the Chartis trial[3], and our own preliminary results using endobronchial valve treatment. The aggregate mean FEV_1, % of predicted (±standard deviation) of the above trial data used were: 33.2±12% versus 47.6±13.7%. With a power of 80% and a 95% probability, we calculated that 28 patients (14 per arm) would have to be randomized. During the study an interim analysis was discussed with, and agreed upon by both the ethics committee and the granting organization (The Netherlands Organization for Health Research and Development). This was done because we observed a higher pneumothorax rate (20% incidence) than previously reported in both the VENT trial (4% incidence) and Chartis trial (8% incidence), and a higher patient dropout than expected. Additionally, because of the fact that the power calculation was based on the assumptions made using post-hoc results, from trials using different patient selection criteria, the power calculations were updated. These were based on our treated subjects who had had 6 months follow-up at that moment (N=17). This analysis showed a lower than expected change in mean FEV_1: 28.3±6.2% of predicted value at baseline to 35.7±10.4% of predicted value at 6 months of follow up. With a power of 80% and a 95% probability, a total of 2x23 patients had to be randomized and evaluable. In light of the dropout rate and to collect more safety data especially for the occurrence of pneumothorax and its management, a total number of 68 patients (34 per arm) were agreed upon as necessary.

Baseline outcomes

Two-sample t-test and Fisher's Exact Test were performed to test for differences between endobronchial valve group and Control group at baseline.

Primary effectiveness outcomes

Primary effectiveness outcomes were improvement in FEV_1, forced vital capacity, and 6 minute walk distance for the endobronchial valve treatment group compared to controls at 6 months follow-up in the 'intention to treat' population. Clinical response was defined using established minimal clinically important differences (MCID). The change in outcomes from baseline to 6 months follow up between groups were compared using an two-sample t-test or if there was no normal distribution the Wilcoxon signed rank test was used. The primary endpoints consisted of 3 outcome measures. We adjusted for multiple comparisons with the Bonferonni correction. (Alpha/3; P value=0.0167). P values < 0.0167 were considered statistically significant for the primary effectiveness outcomes. Paired t-tests or if there was no normal distribution the Wilcoxon signed rank test were used to compare the outcomes in change from baseline at 6 months follow-up in each group. Patient responder rates were calculated by counting the number of patients who reached the minimal clinically important

difference. Fisher's Exact Test was performed to test for differences between groups. The Primary effectiveness outcomes are presented in the manuscript as intention-to-treat results. The intention-to-treat results were based on all randomized subjects (endobronchial valve N=34; Control N=34).

Intention-to-treat analyses of the primary effectiveness outcomes and MCIDs

The intention-to-treat analyses were performed for the primary endpoints (FEV_1, forced vital capacity and distance on 6 minute walk test) and provided in the abstract, the results section, table 3 and figure 2a of the manuscript. The intention-to-treat analysis was based on all randomized patients, including the patients who had premature study discontinuation. For the intention-to-treat analysis we have imputed the available "after study-exit" PFT data (N=7) from the patients who had an early study-exit and we used multiple imputation in patients (N=2) without available PFT data. This multiple imputation was based on the distribution of change in FEV_1 and forced vital capacity in control patients. We have corrected for age, gender, height and weight. The imputations were done 50 times generating 50 individual imputed values. The individual mean value was used as imputation. This resulted for the endobronchial valve group in N=9 imputations for the intention-to-treat analysis and for the Control group in N=1 (based on available PFT data) for the intention-to-treat analysis. Since no follow-up data on the distance on 6 minute walk test is available for the patients who had a premature study discontinuation, we used multiple imputations of the missing values. This imputation was based on the distribution of change in the distance on 6 minute walk test in control patients. We have corrected for age, gender, height and weight. The imputations were done 50 times generating 50 individual imputed values. The individual mean value was used as imputation. Patients (N=2) who were not able to walk zero change was assigned.[8] This resulted for the endobronchial valve group in N=9 imputations for the intention-to-treat analysis, and for the Control group in N=1 for the intention-to-treat analysis. Based on the intention-to-treat analyses, the responder rates for the primary endpoints were also calculated (responders being defined as those reaching the minimal clinically important difference). Patients who had a premature study discontinuation were counted as "not achieving minimal clinically important difference". The change in outcomes from baseline to 6 months follow up between groups were compared using an two-sample t-test. Bonferroni correction was performed for multiple comparisons for the three primary end points. P values of less than 0.0167, for primary outcomes in the intention-to-treat analyses were considered to indicate statistical significance.

Secondary effectiveness outcomes

Secondary effectiveness outcomes were improvements in FEV_1, forced vital capacity, distance on 6 minute walk test, SGRQ, CCQ and the change from baseline in the volume of the treated lobe on the inspiratory HRCT in the patients who completed the study. Clinical response was defined using established minimal clinically important differences (MCID). P values of less than 0.05 were considered statistically significant for the secondary effectiveness outcomes. Results were calculated based on the patients who provided data at 6 months follow-up. Paired t-tests or if there was no normal distribution the Wilcoxon signed rank test were used to compare the outcomes in change from baseline at 6 months of follow-up in each group. Patient responder rates were calculated by counting the number

of patients who reached the minimal clinically important difference. Fisher's Exact Test were performed to test for differences between groups. The secondary effectiveness outcomes are presented in the manuscript as 'outcomes among patients who completed the study'. These 'outcomes among patients who completed the study' were based on the patients who provided data on the primary endpoints at 6 months follow-up (in the endobronchial valve group patients who retained the endobronchial valve treatment). In the figures and tables we have presented the number of patients who completed the study for each outcome.

Analyses among patients who completed the study
The 'outcomes among patients who completed the study' were performed for the primary, secondary and other outcomes and provided in the results section of the manuscript and in the supplementary appendix. Results were calculated based on the patients who completed the 6 months follow-up visit and provided data on the primary endpoints at 6 months follow-up. Patients who had prematurely discontinued the study were not counted in this analyses.

Safety outcomes
Safety was assessed by collecting all adverse events up to study-exit. For patients in the endobronchial valve group up to 6 months after randomization and for patients in the control group up to 6 months after randomization and up to 6 month as after Cross-over endobronchial valve treatment. Fisher's Exact Test was performed for calculation of the difference in number of adverse events between endobronchial valve group and Control group.

Chartis assessment and endobronchial valve treatment

The Chartis assessment was performed at baseline. Table S1a presents the "difficulties" we have observed during the Chartis assessment. In case that the Chartis assessment was inconclusive, we repeated the assessment in the same session until a conclusive outcome was obtained. In case of persistent problems to obtain a good Chartis read-out of the target lobe, or in case of a so called "no-flow" situation in one of the lower lobes, the assessment was reversed to the ipsilateral lobe. The endobronchial valve treatment was performed in 64 patients. In the endobronchial valve group 34 patients received the endobronchial valve treatment and 30 patients in the Cross-over endobronchial valve group. In table S1b are the results presented of the endobronchial valve treatment procedure.

Table S1a. Chartis assessment results.

	Screenfailures (N=16)	EBV group (N=34)	Control group (N=34)
Chartis assessment median duration time — min. (range)	34 (12 to 65)	25 (5 to 65)	17 (5 to 40)
Chartis assessment details			
Conscious sedation during Chartis assessment— no.(%)	16 (100)	34 (100)	34 (100)
Difficult measurement due to severe secretion — no.(%)	2 (12.5)	6 (17.6)	6(17.6)
Difficult measurement due to coughing — no.(%)	0	1 (2.9)	0
No flow measurable in target lobe — no.(%)	2 (12.5)	7 (20.6)	3 (8.8)
Rupture of the Chartis-balloon — no.(%)	2 (12.5)	2 (5.9)	0

Table S1b. Results of the endobronchial valve treatment procedure.

	ALL EBV (N=64)	EBV group (N=34)	Cross-over (N=30)
Endobronchial valve placement median duration time — min. (range)	**17 (5 to 55)**	18 (6 to 51)	16 (5 to 55)
Total endobronchial valves placed — no.	**278**	152	126
size 4.0-LP — no.(%)	**8 (2.9)**	6 (3.9)	2 (1.6)
size 4.0 — no.(%)	**105 (37.8)**	56 (36.8)	49 (38.9)
size 5.5 — no.(%)	**165 (59.4)**	90 (59.2)	75 (59.5)
Endobronchial valves placed per patient — median no. (range)	**4 (1 to 7)**	4 (2 to 7)	4 (1 to 7)
Post-endobronchial valve procedure hospital stay — median days (range)	**1 (1 to 31)**	1 (1 to 13)	2 (1 to 31)
General anesthesia during endobronchial valve placement — no.(%)	**55 (85.9)**	26 (76.5)	29 (96.6)
Conscious sedation during endobronchial valve placement — no.(%)	**9 (14.1)**	8 (23.5)	1 (3.3)
Target lobe for endobronchial valve treatment			
Right Upper lobe — no.(%)	**7 (10.9)**	4 (11.8)	3 (10.0)
Middle lobe — no.(%)	**1 (1.6)**	0	1 (3.3)
Right Lower lobe — no.(%)	**11 (17.2)**	4 (11.8)	7 (23.3)
Left Upper lobe — no.(%)	**17 (26.6)**	11 (32.4)	6 (20.0)
Left Lower lobe — no.(%)	**17 (26.6)**	9 (26.5)	8 (26.7)
Right Upper + Middle lobe — no.(%)	**11 (17.2)**	6 (17.6)	5 (16.7)

Table S2. Efficacy outcomes among patients who completed the study (EBV group and Cross-over EBV group).

		EBV group	Cross-over EBV group
PRIMARY AND SECONDARY OUTCOME			
Forced expiratory volume in 1 second		N=25	N=26
	— ml	216 (128 to 304)	173 (120 to 226)
	— %	26.5 (16.3 to 36.4)	24.6 (15.6 to 33.6)
	MCID (+10%) responder rate	**72%**	**73%**
Forced vital capacity		N=25	N=26
	— ml	529 (309 to 748)	485 (279 to 692)
	— %	22.0 (12.6 to 31.5)	22.9 (12.7 to 33.1)
Distance on 6 minute walk test		N=23	N=25
	— meter	92 (64 to 120)	50 (34 to 67)
	— %	30.0 (18.5 to 41.4)	15.3 (9.9 to 20.6)
	MCID (+26 meter) responder rate	**87%**	**68%**
St George's Respiratory Questionnaire		N=24	N=25
	— points	-17.39 (-24.75 to -10.02)	-14.3 (-201 to -8.3)
	MCID (-4 points) responder rate	**79%**	**80%**
Clinical COPD Questionnaire		N=24	N=25
	— points	-0.87 (-1.25 to -0.31)	-0.73 (-1.02 to -0.44)
	MCID (-0.4 points) responder rate	**63%**	**64%**
Target lobar volume measured on CT-scan¥		N=25	N=26
	— ml	-1366 (-3604 to -28)	-1376 (-1650 to -1101)
	MCID (-350 ml) responder rate	**88%**	**96%**
OTHER OUTCOME		N=24	N=25
Total lung capacity	— ml	-384 (-512 to -256)	-326 (-487 to -164)
Residual volume	— ml	-865 (-1166 to -563)	-670 (-917 to -424)
	MCID (-430 ml) responder rate	**71%**	**64%**
Residual volume/Total lung capacity	— %	-8.5 (-11.1 to -5.8)	-6.9 (-9.6 to -4.1)
	MCID (-4%) responder rate	**63%**	**60%**

Paired t-test was used for calculation of the mean differences, P values and 95% confidence intervals. All P-values <0.001. ¥Wilcoxon signed rank test was used for calculation of the median difference, P values and range in target lobar volume on CT scan. Two-sample t-test was performed for calculation of the between-group differences. All P values >0.05 between EBV group versus Cross-over except for distance on 6 minute walk test (meter: P value 0.009; %: P value 0.017). MCID denotes minimal clinically important difference.

Post-hoc CT scan analysis.
On the baseline inspiratory HRCT scan (slice thickness of 1.0 mm, SOMATOM Sensation 64 eco, Siemens Healthcare, USA), computerized quantifications were performed on the entire CT data-set (Thirona lung quantification 15.01, Thirona BV, Nijmegen, the Netherlands). The lobes were automatically segmented, visually inspected and edited where needed. Both lobar volumes and percentage of voxels below -950 Hounsfield units, an indicator of the fraction of emphysematous lung were calculated. In this study, -950 Hounsfield units was used as a density threshold for emphysema quantification because of the thin section volumetric chest CT scans used.

Heterogeneity
The percentage of heterogeneity was defined as the difference the percentage of voxels of less than −950 Hounsfield units between the target lobe and the ipsilateral adjacent non-target lobe.

The degree of heterogeneity was defined as follow:
Heterogeneous ≥ 15%
Homogeneous < 15%

Table S3. Between-group (EBV versus control) difference homogeneous and heterogeneous emphysema among the patients who completed the study.

	Homogeneous		Heterogeneous	
	EBV N=16 versus control N=18	P value	EBV N=9 versus control N=15	P value
FEV_1				
— ml	127 (8 to 247)	0.037	291 (189 to 392)	<0.001
— %	15 (2 to 28)	0.028	36 (24 to 48)	<0.001
Forced vital capacity				
— ml	255 (-87 to 598)	0.139	712 (460 to 965)	<0.001
— %	9 (-4 to 22)	0.157	30 (16 to 44)	<0.001
Residual volume				
— ml	-715 (-1108 to -322)	0.001	-997 (-1382 to -612)	<0.001
— %	-16 (-22 to -9)	<0.001	-20 (-27 to -13)	<0.001
Distance on 6 minute walk test				
— meter	107 (69 to 145)	<0.001	108 (71 to 145)	<0.001
SGRQ Total score				
— points	-12 (-21 to -4)	0.008	-19 (-31 to -6)	0.005

EBV denotes endobronchial valve. Two-sample t-test was used for calculation of the between-group mean differences, P values and 95% confidence intervals.

Table S4. Serious adverse events up to 6 months follow-up in the EBV group and Cross-over EBV group.

	EBV group (N=34)	Cross-over EBV (N=30)
Number of serious events	**23**	**28**
Death[§]	1 (2.9)	0
COPD exacerbation with hospitalization	4 (11.8)	3 (10.0)
Pneumonia	2 (5.9)	1 (3.3)
Pneumothorax total	6 (17.6)	8 (26.7)
Without drainage (stable ≤ 14 days after onset)	1 (5.9)	3 (10.0)
With drainage (stable ≤ 14 days after onset)	2 (5.9)	2 (6.7)
Pneumothorax with temporary valve removal[≠]	1 (2.9)	2 (6.7)
Recurrent pneumothorax with permanent removal of all valves[†]	1 (2.9)	1 (3.3)
Recurrent pneumothorax with temporary valve removal, back-placement and permanent removal of all valves	1 (2.9)	0
Torsion of the bronchus[℮]	2 (5.9)	0
Pneumonia distal to valve[‡]	1 (2.9)	0
Complaints (increased sputum, dyspnea, and/or coughing) without patient perceived treatment benefit	2 (5.9)	2 (6.7)
Valve migration	2 (5.9)	1 (3.3)
Valve expectoration	0	3 (10.0)
Valve dislocation due to formation of granulation tissue	1 (2.9)	0
Complaints (increased sputum, dyspnea and/or coughing)	1 (2.9)	0
Non-Pulmonary event		
Stroke	1 (2.9)	1 (3.3)
Paroxysmal atrial fibrillation	0	1 (3.3)

[§]One subject died 58 days post endobronchial valve treatment due to respiratory failure end-stage COPD. [≠]Temporary valve removal to expand the endobronchial valve target lobe; pneumothorax resolved and at 49 days the valve was placed back. [†]Temporary valve removal to expand the endobronchial valve target lobe; pneumothorax resolved and at 61 days the valve was placed back. [℮]Two subjects had low oxygen saturation and dyspnea complaints after endobronchial valve treatment left upper lobe; CT scan confirmed torsion of left lower bronchus; valves were removed in both cases at 14 days with complete recovery after removal. [‡]Post-obstruction pneumonia in treated lobe onset 163 days after treatment; valves were removed and subject recovered.

Table S5. Non-serious adverse events up to 6 months follow-up.

	EBV group (N=34)	Control (N=34)	P value	All EBV (N=64)
Number of events	**59**	**35**	**<0.001**	**95**
Atelectasis syndrome	0 (0)	NA	NA	1 (1.6)
Back pain	0 (0)	0 (0)	NA	1 (1.6)
Bleeding during EBV procedure (mild)	1 (2.9)	NA	NA	1 (1.6)
Bursitis	0 (0)	0 (0)	NA	1 (1.6)
Bronchitis	1 (2.9)	0 (0)	1.000	1 (1.6)
Chest pain (noncardiac)	10 (29.4)	0 (0)	**0.001**	13 (20.3)
Colorized sputum	3 (8.8)	0 (0)	0.239	3 (4.7)
Common cold	3 (8.8)	4 (11.8)	1.000	3 (4.7)
COPD exacerbation without hospitalization	15 (44.1)	17 (50.0)	0.808	23 (35.9)
Cough	9 (26.5)	1 (2.9)	**0.013**	16 (25.0)
Desaturation	0 (0)	0 (0)	NA	1 (1.6)
Diarrhea	1 (2.9)	1 (2.9)	1.000	1 (1.6)
Dyspnea	4 (11.8)	3 (8.8)	1.000	6 (9.4)
Edema	0 (0)	1 (2.9)	1.000	0 (0)
Fever e.c.i.	0 (0)	0 (0)	NA	1 (1.6)
Flue	3 (8.8)	1 (2.9)	0.614	3 (4.7)
Frozen shoulder	0 (0)	1 (2.9)	1.000	0 (0)
Headache	1 (2.9)	0 (0)	1.000	1 (1.6)
Hemoptysis (mild)	1 (2.9)	0 (0)	1.000	1 (1.6)
Hypertension	0 (0)	3 (8.8)	0.239	0 (0)
Mamma carcinoma	0 (0)	1 (2.9)	1.000	0 (0)
Muscle pain	0 (0)	0 (0)	NA	1 (1.6)
Nausea	1 (2.9)	0 (0)	1.000	1 (1.6)
Open wound leg	0 (0)	0 (0)	NA	1 (1.6)
Peripheral arterial insufficiency	1 (2.9)	0 (0)	1.000	1 (1.6)
Pleural fluid in treated lung (without intervention)	1 (2.9)	NA	NA	1 (1.6)
Pneumonia without hospitalization	0 (0)	0 (0)	NA	1 (1.6)
Pseudomonas aeruginosa infection in sputum	0 (0)	0 (0)	NA	1 (1.6)
Sciatica	0 (0)	0 (0)	NA	1 (1.6)
Sore throat	2 (5.9)	0 (0)	0.493	2 (3.1)
Sprained ankle	0 (0)	1 (2.9)	1.000	1 (1.6)
Sputum production increased	2 (5.9)	0 (0)	0.493	5 (7.8)
Tachycardia	0 (0)	0 (0)	NA	1 (1.6)
Upper airway tract infection	0 (0)	0 (0)	NA	1 (1.6)
Wrist fracture	0 (0)	1 (2.9)	1.000	0 (0)

Two-sided Fisher's Exact Test was used for calculation of the difference in adverse events between EBV group and control.

Pneumothoraces

The large reduction in lung volume with subsequent positive outcome was accompanied by adverse effects, especially pneumothoraces, which were manageable using regular care with chest-tube drainage, but sometimes required repeat bronchoscopies. The pneumothorax frequency in the Endobronchial valve group (34 patients) was 17.6% (6 patients) and in the overall patient group treated with endobronchial valve (Endobronchial valve group + Cross-over endobronchial valve; 64 patients) was 21.9% (14 patients).

Re-bronchoscopy

During the entire study in N=64 treated patients, a re-bronchoscopy with valve replacement was performed in 8 patients: 3 patients after valve expectoration, 3 patients after local valve migration, in 1 patient after valve dislocation due granulation tissue, and in 1 patient due to complaints of increased dyspnea, sputum and coughing without treatment benefit. In this patient were the valves removed from the right upper lobe and middle lobe and replaced to the left upper lobe 56 days after endobronchial valve treatment.

Permanent removal of valves

Two subjects had low oxygen saturation and dyspnea complaints after endobronchial valve treatment of the left upper lobe. At CT scan and during re-bronchoscopy we observed a slight torsion of the left lower main bronchus. The valves were removed with complete recovery after removal. Two patients had increased sputum, dyspnea and coughing complaints without treatment benefit. The valves were removed at 35 days and in the other patient at 77 days after endobronchial valve treatment. Two patients had complaints and after bronchoscopy valve dislocation due to formation of granulation tissue was observed. The valves were once replaced, in the first patient at 57 days and in the second patient at 82 days after treatment. These two patients also had increased sputum, dyspnea and coughing complaints and all valves were removed at respectively 166 days and 147 days after the first endobronchial valve treatment. After removal of the valves the complaints resolved. In one patient we observed 162 days post endobronchial valve treatment an obstruction pneumonia. The endobronchial valves were removed at 201 days after endobronchial valve treatment and patient recovered.

Premature study discontinuation

At 6 months, the rate of study discontinuation was greater in the endobronchial valve group as compared with the control group. Of the 34 patients who received endobronchial valve treatment, 9 (26.5%) patients were not able to complete 6 months follow-up. Of these 9 patients, 1 died, 1 patient was lost to follow-up after hospitalization due to a viral infection, and in 7 patients the valves were removed for the following reasons: one because of an obstruction pneumonia, two because of a recurrent pneumothorax, two because of a torsion of the left lower lobe bronchus after left upper lobe treatment, and two because of significant complaints of increased dyspnea and sputum production with lack of efficacy. In the Control group 1 patient (2.9%) voluntary withdrew. At 6 months, in the endobronchial valve group 2 patients did not perform the 6 minute walk distance test: one due to peripheral arterial insufficiency and one due to walking problems after a cerebral vascular accident. In the Cross-over endobronchial valve group, in 3 patients no lobar occlusion could be achieved with endobronchial valve due to local anatomical reasons. Of the 30 patients who received endobronchial valve treatment in the Cross-over, 4 (13.3%) patients were not able to complete 6 months follow-up because of valve removal: two because of a recurrent pneumothorax, and two because of valve dislocation due to granulation tissue. At 6 months follow-up in the Cross-over endobronchial valve group 1 patient did not perform the 6 minute walk test due to walking problems after a cerebral vascular accident.

Table S6. Reasons for study discontinuation.

Reason for study discontinuation	EBV group (N=34)	Control group (N=34)	Cross-over group (N=33)
Voluntary withdrawal	0 (0%)	1 (2.9%)	0 (0%)
Death	1 (2.9%)	0 (0%)	0 (0%)
Investigator withdrawal[#]	1 (2.9%)	0 (0%)	0 (0%)
(sub) segment was not accessible with the study device[§]	NA	NA	3 (9.1%)
Valve removal	**7 (20.6)**	**NA**	**4 (12.1%)**
Valve removal due to complaints and lack of efficacy	2 (5.9%)	NA	0 (0%)
Valve removal due to torsion bronchus	2 (5.9%)	NA	0 (0%)
Valve removal due to recurrent pneumothorax	2 (5.9%)	NA	2 (6.1%)
Valve removal due to pneumonia distal to valve	1 (2.9%)	NA	0 (0%)
Valve removal due to severe granulation tissue around valves	0 (0%)	NA	2 (6.1%)

NA denotes not applicable.[#]Investigator withdrawal; patient could not perform the 6 month follow-up visit due to a long ICU admission with 2 weeks of invasive ventilation due to a COPD exacerbation caused by a documented viral infection.[§](sub) segment was not accessible with the study device. In a few of our patients it was not possible to either reach the RB6a or RB1 segment with the endobronchial valve catheter, and did we have sometimes in these same segments severe problems with a too short Zephyr endobronchial valve 'landing' zone, without any more distal alternative, thus resulting in both situations in the inability to place one of the Zephyr endobronchial valves available. In these cases lobar exclusion could not be achieved, and this was observed during the actual treatment.

There were no deaths related to the trial participation, bronchoscopic intervention, or removal of valves. Two of the trial discontinuation patients died both 1 year after valve removal and study discontinuation: one due to complications after lung volume reduction surgery, and one due to the complications of a severe pneumonia (eight months after valve removal).

Of all, except from one patient, we obtained post study discontinuation spirometry from the patients who had premature study discontinuation. The results are presented in the table below.

	Baseline (N=12)	Post discontinuation follow-up (N=11)	P value
FEV_1, L	0.77 (0.57 – 1.77)	0.80 (0.54 – 1.66)	0.197
FVC, L	3.05 (2.03 – 5.10)	2.94 (2.15 – 4.21)	0.575

Aggregate spirometry data of post study discontinuation patients who were treated with endobronchial valve. FEV_1: Forced expiratory flow in one second. FVC: Forced vital capacity. Values given as median (min-max). The difference between baseline and follow-up was calculated using the non-parametrical Wilcoxon Signed Ranks Test using IBM/SPSS version 22.

References

1. Miller MR, Crapo R, Hankinson J, et al. General considerations for lung function testing. Eur Respir J 2005;26:153-61.

2. Herth FJ, Noppen M, Valipour A, et al. Efficacy predictors of lung volume reduction with Zephyr valves in a European cohort. Eur Respir J 2012;39:1334-42.

3. Herth FJ, Eberhardt R, Gompelmann D, et al. Radiological and clinical outcomes of using Chartis to plan endobronchial valve treatment. Eur Respir J 2013;41:302-8.

4. Herth FJ, Eberhardt R, Gompelmann D, et al. Radiological and clinical outcomes of using Chartis to plan endobronchial valve treatment. Eur Respir J 2013;41:302-8.

5. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J 2005;26:319-38.

6. Stocks J, Quanjer PH. Reference values for residual volume, functional residual capacity and total lung capacity. ATS Workshop on Lung Volume Measurements. Official Statement of The European Respiratory Society. Eur Respir J 1995;8:492-506.

7. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111-7.

8. Sciurba FC, Ernst A, Herth FJ, et al. A randomized study of endobronchial valves for advanced emphysema. N Engl J Med 2010;363:1233-44.

CHAPTER

6

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

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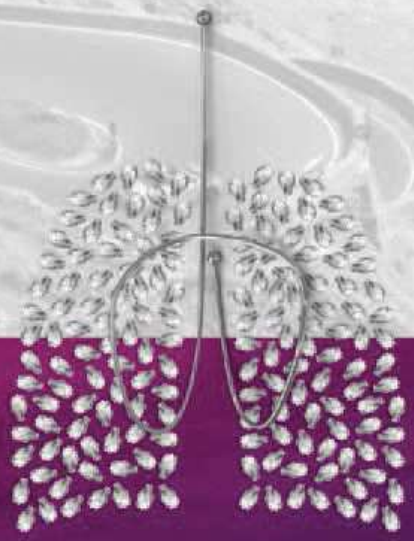

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ABSTRACT

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

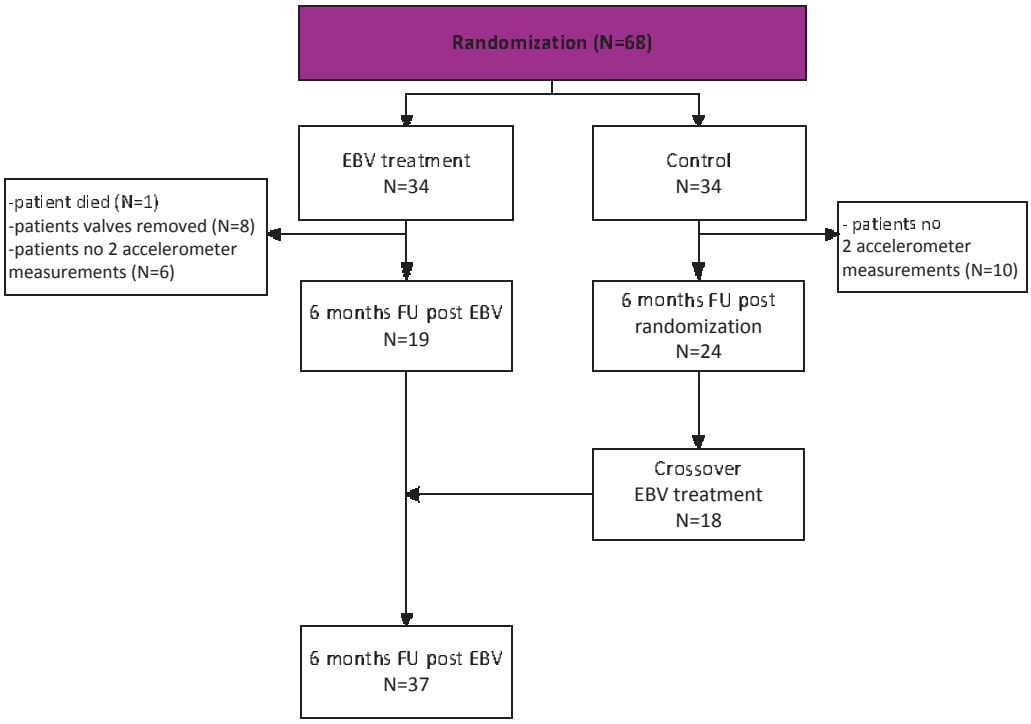
Characteristics of the 43 patients who had evaluable accelerometer data are shown in table 1 and the flow of patients through the study is shown in figure 1. Of these 43 patients, 19 patients were treated with the endobronchial valve treatment and 24 patients received standard medical care. No significant 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)

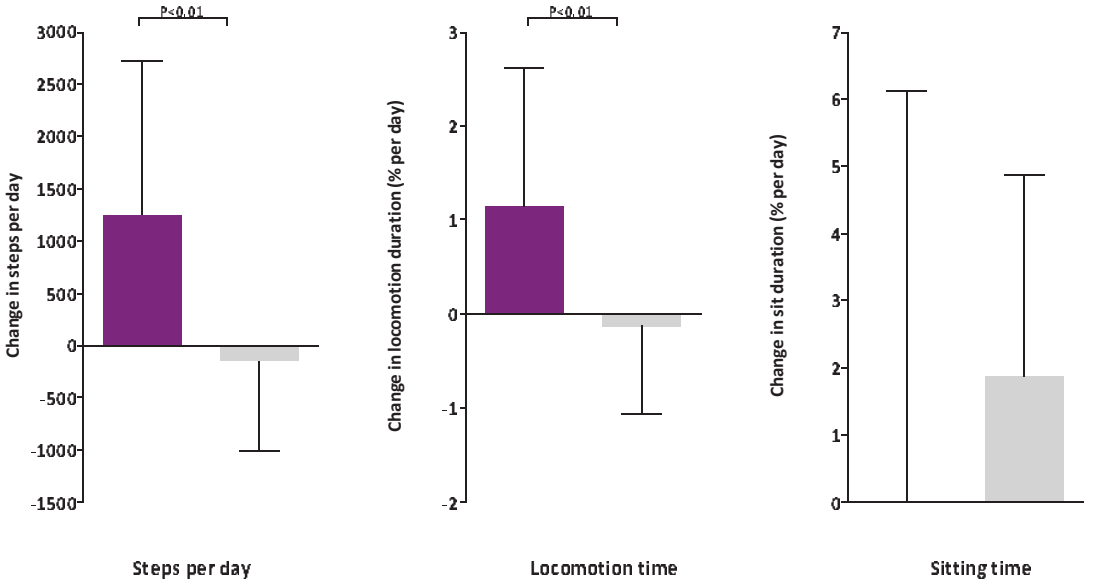
The changes in physical activity and other parameters between baseline and 6 months follow up including the crossover patients are shown in table 3. The individual patient data of the change in steps per day is shown in figure 3. After endobronchial valve treatment patients significantly improved compared 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.



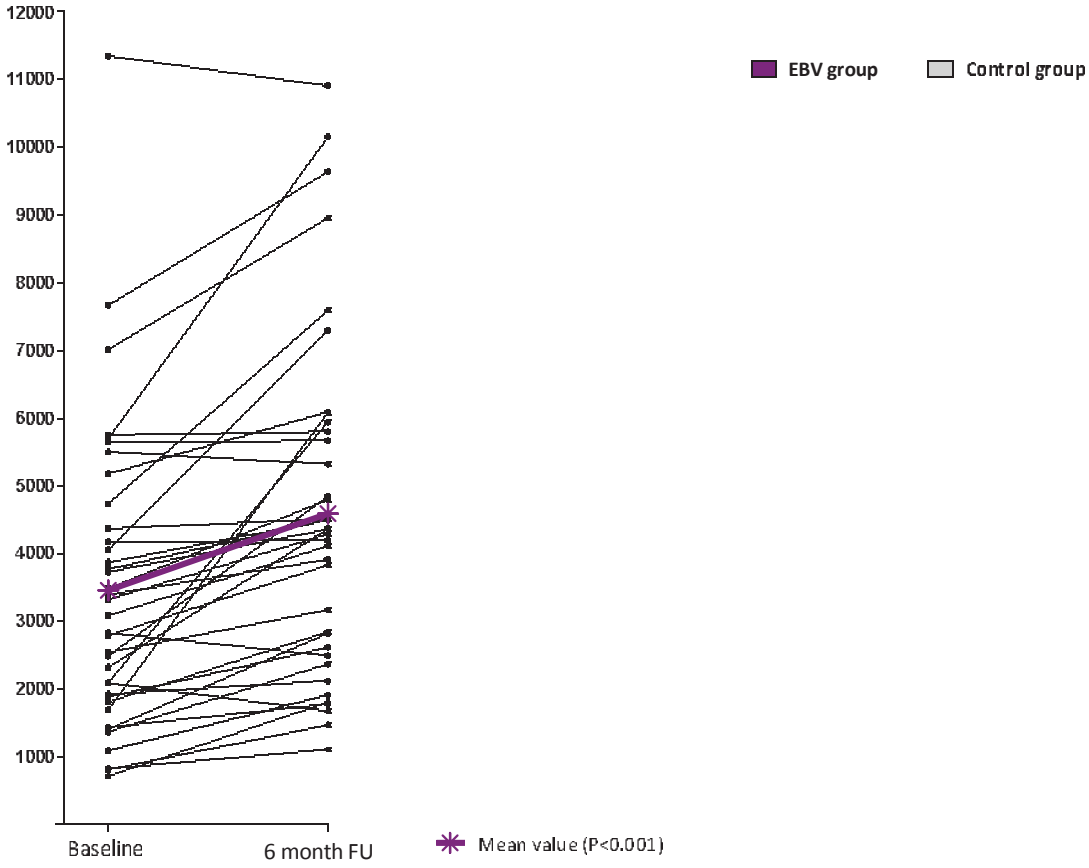


Table 3. Change in clinical characteristics at 6 months after endobronchial valve treatment (N=37).

	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.

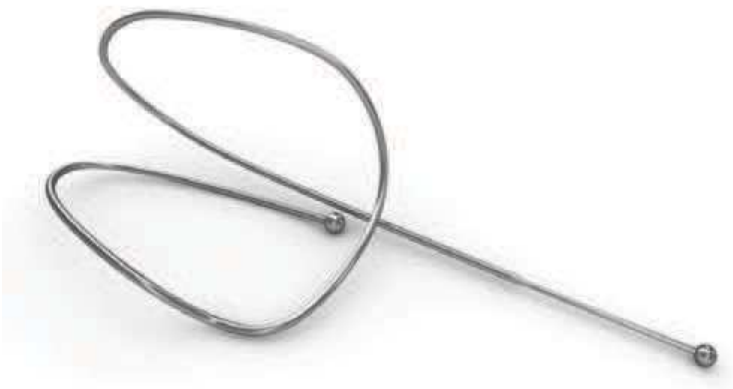
27. Fishman A, Martinez F, Naunheim K, et al., National Emphysema Treatment Trial Research Group. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. N Engl J Med 2003; 348: 2059-2073.

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.



CHAPTER

7

Bronchoscopic lung volume reduction coil treatment of patients with severe heterogeneous emphysema

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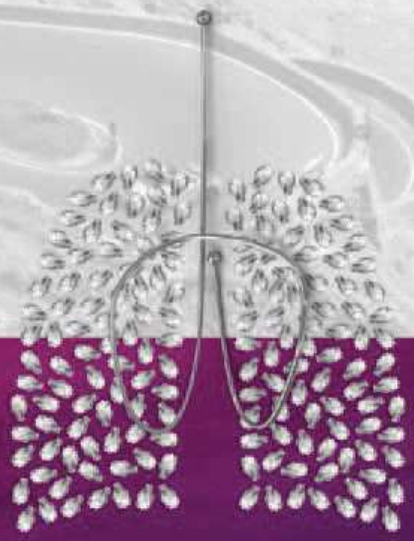


Adapted from

Chest 2012;142:574-82.

ABSTRACT

Background
The lung volume reduction coil, a new experimental device to achieve lung volume reduction by bronchoscopy in patients with severe emphysema, works in a manner unaffected by collateral airflow. We investigated the safety and efficacy of lung volume reduction coil treatment in patients with heterogeneous emphysema.

Methods
In this prospective cohort pilot study, patients were treated bronchoscopically with nitinol coils under fluoroscopic guidance in either one procedure or two sequential procedures. Follow-up tests included the St. George's Respiratory Questionnaire (SGRQ), pulmonary function testing, and the 6 minute walk test.

Results
Twenty-eight lung volume reduction coil procedures were performed in 16 patients (baseline FEV_1, 28±7.6% of the predicted value). Four patients were treated in one lung, and 12 patients were treated in both lungs. A median of 10 (5-12) coils was placed per lung in 36.5 (20-60) minutes.

Adverse events rated as possibly related to either the device or the procedure, 30 days after treatment were pneumothorax (N=1), pneumonia (N=2), COPD exacerbation (N=6), chest pain (N=4), and mild (<5 mL) hemoptysis (N=21). From 30 days to 6 months, the adverse events that occurred were pneumonia (N=3) and COPD exacerbation (N=14). All events resolved with standard care.

Six months after lung volume reduction coil treatment, there were significant improvements in SGRQ by -14.9±12.1 points (with 11 patients improving by >4 points), in FEV_1 by +14.9±17.0%, in forced vital capacity by + 13.4±12.9%, in residual volume by -11.4±9.0%, and in distance on the 6 minute walk test by + 84.4±73.4 meter (all $P < 0.005$).

Conclusion
Lung volume reduction coil treatment is a promising technique for the treatment of patients with severe heterogeneous emphysema. The treatment is technically feasible and results in significant improvements in pulmonary function, exercise capacity, and quality of life, with an acceptable safety profile.

INTRODUCTION

COPD is an incurable and highly prevalent disease.[1] Patients with advanced emphysema suffer from dyspnea because of decreasing elastic recoil of the lungs, which, along with airway collapse and increased expiratory flow resistance, causes static and dynamic hyperinflation. This hyperinflation is associated with inefficient respiratory muscles, leading to dyspnea and mortality disproportionate to changes in FEV_1.[2,3]

There is currently no cure for emphysema, and the goal of medical treatment is primarily to relieve symptoms and reduce exacerbations using inhaled bronchodilators, anti-inflammatory drugs, proper nutrition, rehabilitation, and supplemental oxygen.[1] Only for a very small subset of patients with COPD are invasive surgical procedures such as lung volume reduction surgery and lung transplantation available.[4] Although the concept of lung volume reduction surgery is excellent, the referral of patients is severely influenced by significant early morbidity.[5] Lung transplantation is even more invasive and, in addition, is limited by donor shortage and unclear survival benefits in COPD.[6]

During the past few years, there has been great interest in bronchoscopic lung volume reduction using different designs of one-way endobronchial valves as an alternative to lung volume reduction surgery.[7,8,9] However, the efficacy of these treatments is limited by both the presence of collateral airflow from adjacent segments, which inhibits the volume reduction of the treated lobe, and the technical difficulty of accurately placing these endobronchial valves in difficult airways anatomy.[9]

At present, efforts are underway to identify responders to one-way endobronchial valve treatment by assessing collateral ventilation.[10] However, the Endobronchial Valve for Emphysema Palliation Trial (VENT) results showed that the majority of patients with heterogeneous emphysema will not benefit from treatment with endobronchial valves,[9] indicating the need for bronchoscopic lung volume reduction treatments that work independently of collateral flow and are less reliant on the very accurate placement of an air sealing device.

To our knowledge, we reported the first study in humans demonstrating the feasibility of bronchoscopic lung volume reduction using a nitinol lung volume reduction coil (LVR-coil) in patients with severe emphysema.[11] In that pilot study, we treated eight patients with severe homogeneous emphysema and three patients with severe heterogeneous emphysema with a median of five coils per lobe. Clinically meaningful improvements were observed only in the heterogeneous patients. In the current study, we further investigate the feasibility, safety, and efficacy of the LVR-coil treatment, specifically in patients with severe heterogeneous emphysema.

METHODS

Study design and population

Patients with heterogeneous emphysema were eligible for this prospective cohort trial. The main inclusion and exclusion criteria are shown in box 1.[12] Heterogeneity was assessed visually by the principal investigator on sagittal reconstructions of a full inspiratory, thin-slice chest CT scan. Emphysema destruction was thereafter digitally assessed by calculating the percentage relative area of destruction below -950 Hounsfield units between the ipsilateral upper and lower lobes of the target lung (Pulmo 2.1; Medis[13,14]). The determination of heterogeneous emphysema was based on identifying disproportionate destruction in the targeted lobe compared with the non-targeted lobe. In this pilot phase, we did not include patients with >75% destruction of the upper lobes. The initial protocol included a 3 month follow-up. During the study this was extended to 6 months, for which the subjects gave additional written informed consent. This study was approved by the University Medical Center of Groningen medical ethics committee (NL26560.042.09).

Box 1. The main inclusion and exclusion criteria.

Inclusion criteria

- FEV_1 <45% of predicted
- Total lung capacity >100% of predicted
- Modified medical research council dyspnea score (mMRC) >1
- Non-smoker for more than eight weeks
- Heterogeneous emphysema

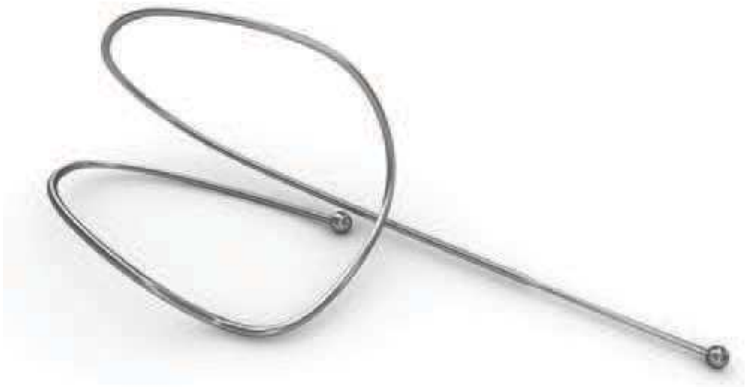
Exclusion criteria

- Change in FEV_1 > 20% post-bronchodilator
- Diffusion capacity < 20% predicted
- Right ventricular pressure >50mmHg
- >3 hospitalizations due to COPD exacerbations in the previous 12 months
- Clinically significant bronchiectasis
- Previous lung surgery, or a giant bulla (> 1/3 of the lung volume)
- Distance on 6 minute walk test <140 meter
- Any use of clopidogrel or coumarines
- Any disease that might compromise survival (such as active lung cancer), or any other disease likely to interfere with completion of study, follow up assessments or that would adversely affect outcomes

Lung volume reduction coils and the procedure

The lung volume reduction coils (RePneu; PneumRx, Inc.) are made from preformed nitinol wire (figure 1), which causes parenchymal compression and is made in a range of lengths (70 to 200 mm) to accommodate airways of different sizes.

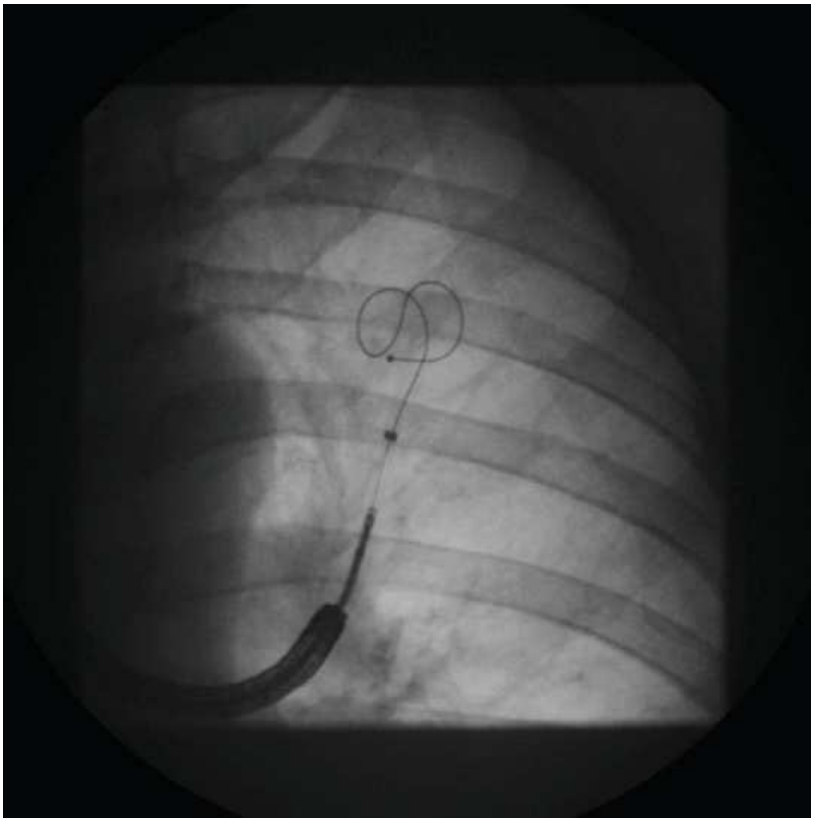
Figure 1. Lung volume reduction coil.



The lung volume reduction coil is bronchoscopically delivered straight into (sub) segmental airways and recovers to the predetermined shape upon deployment.

The procedure in this study was performed as described previously,[11] with more coils placed per lobe and by using a standardized segmental treatment algorithm independent of specific CT scan findings (right upper lobe, RB2-RB1-RB3; left upper lobe, LB1/2-LB3-LB4), leaving LB5 untreated because of its proximity to the heart. During bronchoscopy, first the guidewire is advanced into the desired airway under fluoroscopic guidance. A catheter is passed over the guidewire and aligned with the distal tip of the guidewire at 15 mm from the pleura. The length of the airway is measured using radiopaque markers to choose the coil length. The guidewire is then removed, and a straightened coil, preloaded into a cartridge, is pushed forward through the catheter with a biopsy forceps under fluoroscopic guidance. Next, the catheter is removed while the coil is held in place and regains its original shape. Finally, the coil is released from the biopsy forceps. These steps then are repeated for every following coil to be placed. The coil can be removed or repositioned by reversing this implantation process. In this study, the lung volume reduction coil procedure was performed under general anesthesia using a 9.0 mm endotracheal flexible tube and flexible bronchoscope (Olympus BF 180; 2.8 mm working channel, 6.0 mm outer diameter) under fluoroscopy guidance (figure 2). Following recovery from anesthesia, patients stayed one night in the hospital for observation.

Figure 2. Actual deployment of a coil in the LB_1 segment under fluoroscopic guidance.



Follow-up

Safety was assessed by recording all adverse events that occurred. Adverse events were divided into those occurring during the first 30 days after lung volume reduction coil treatment, the period we regarded to be related to the actual procedure, and those occurring during the follow-up period from 1 to 6 months. The primary efficacy variable was change in respiratory related quality of life as measured by the St. George's Respiratory Questionnaire (SGRQ) total score.[15] Additionally, pulmonary function testing (spirometry, body plethysmography, and diffusion capacity) and a 6 minute walk test were performed according to ATS/ERS guidelines.[16,17] Follow-up was performed at 1 and 3 months after the first and second treatment and at 6 months after the final treatment.

Statistics

Results are presented as means ± standard deviation or medians (range) when appropriate. Paired t-tests were used for comparison of results before and after lung volume reduction coil treatment. Microsoft Office Excel 2003 (Microsoft Corporation) and GraphPad Prism (GraphPad Software, Inc) for Windows 4.0 were used for statistical analysis.

RESULTS

Patients

Between April 2009 and March 2010, we recruited 17 and finally treated 16 patients with heterogeneous emphysema (see figure 3 for study flowchart and table 1 for patient demographics and baseline characteristics). The mean emphysema CT scan destruction scores for the right upper lobe were 54.4% (±13.8%) versus 21.2% (±10.4%) for the right lower lobe, and 47.8% (±14.5%) for the left upper lobe versus 18.1% (±9.9%) for the left lower lobe (both differences, $P < 0.0001$).

Twelve patients were treated bilaterally in two sequential procedures, and four patients received lung volume reduction coil treatment of one lung (two patients with only one eligible lung, one patient with underlying coronary artery disease in whom we decided not to treat the second lung, and one patient who improved to such a large degree that we decided not to treat the second lung).

Figure 3. Study flowchart.

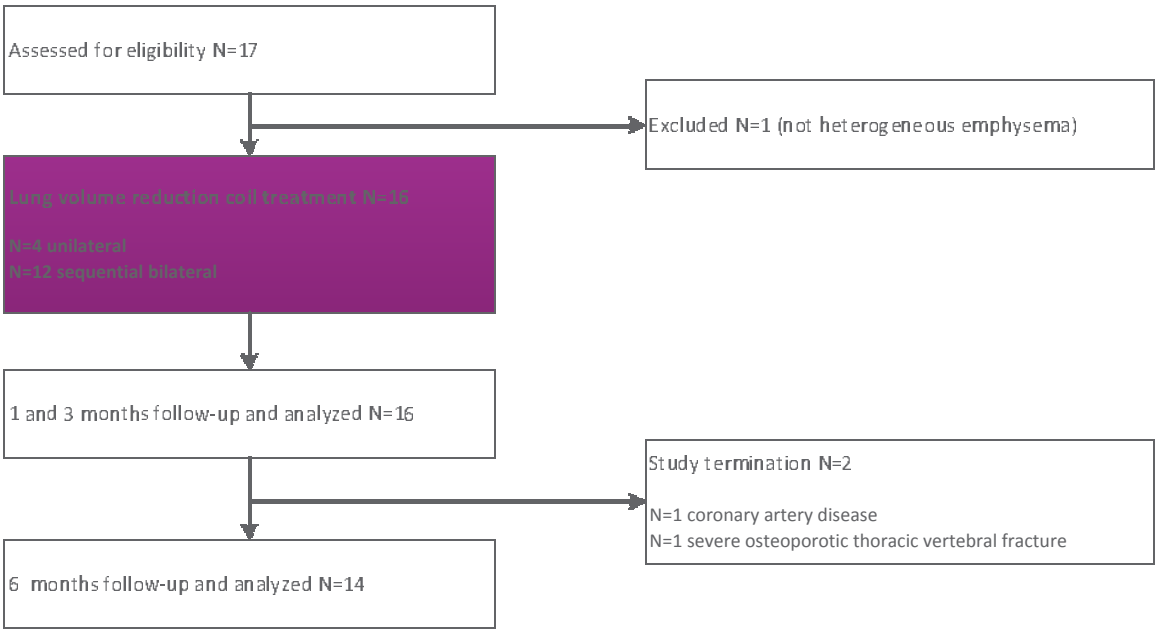


Table 1. Patient demographics and baseline characteristics (N=16).

Characteristic	
Age, years	58±7.3
Female/Male	12/4
Packyears	31±13
BMI, kg/m^2	24.9±3.0
FEV_1, Liter	0.72±0.16
FEV_1, % of predicted value	28.7±7.1
FVC, Liter	2.63±0.83
FVC, % of predicted value	83.1±14.4
RV, Liter	4.42±0.98
RV, % of predicted value	225±43
TLC, Liter	7.32±1.55
TLC, % of predicted value	135±11
Ratio of RV to TLC, %	60.5±6.4
$PaCO_2$, kPa	5.7±0.8
PaO_2, kPa	9.2±1.4
Distance on 6 minute walk test, meter	338±112
mMRC, points	2.8±0.7
SGRQ, points	64±9
BODE index	5.7±1.6
Previous pulmonary rehabilitation	13
Use of home oxygen	4
Medication use	
short acting $beta_2$- agonists	11
long acting $beta_2$- agonists	14
ipratropium	7
tiotropium	13
inhaled corticosteroids	15
acetylcysteine	6
theophylline	2
maintenance prednisolone	6
maintenance antibiotics	5

Data are presented as mean ± standard deviation or absolute numbers.

Lung volume reduction coil procedure

In 28 procedures, 260 coils; median 10 coils (range, 5-12) per procedure were placed. A median time of 36.5 minutes (range, 20-60 minutes) per lung was recorded. No peri-procedural technical events occurred, and all coils could be placed as planned. Follow-up chest radiographs made on day 1, and on 1, 3, and 6 months post procedure (see figure 4 for an example) showed no migration of coils. In four patients, a partial atelectasis due to the coils could be observed on the follow-up radiographs. Of the 260 coils placed in this study, none had to be replaced or removed (see table 2 for all procedural results[18]).

Figure 4. Thoracic radiograph showing the coils in situ in all segments of both upper lobes.

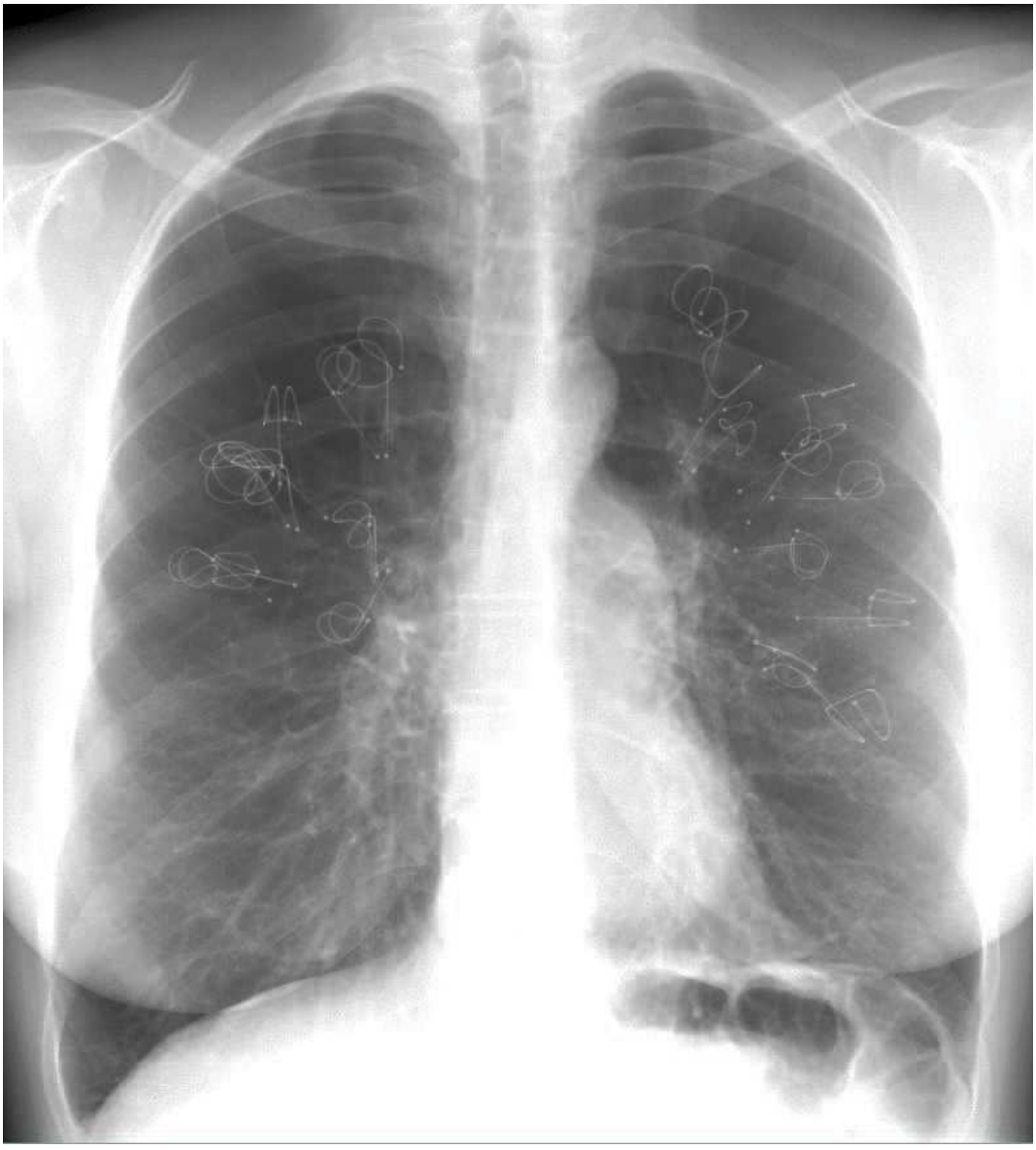


Table 2. Procedural results.

	Number
Lung volume reduction coil procedures, number	28
Unilateral coil procedure RUL/LUL, number of patients	2/2
Bilateral coil, number of patients	12
Procedure time, minute (median, range)	36.5 (20-60)
Total coils placed, number	260
Coils placed per subject, number (median, range)	10 (5-12)
Coils placed per segment, number	
RB_1 (right-apical)	38
RB_2 (right-posterior)	37
RB_3 (right-anterior)	59
$LB_{1/2}$ (left-apicoposterior)	54
LB_3 (left-anterior)	63
LB_4 (left-superior lingular)	9
Coil lengths used, number of coils	
85mm	1
100mm	170
125mm	86
150mm	3

Procedural results are given as absolute numbers and median (range) where indicated. LUL: left upper lobe; RUL: right upper lobe.

Safety

All patients received general anesthesia, uneventfully. In addition, no adverse events during the bronchoscopy or actual coil placements were observed. In 28 procedures, one (< 5%) pneumothorax occurred 1 hour after the bronchoscopy and resolved quickly with a chest tube in 1 day. In 12 patients, mild hemoptysis occurred in 21 procedures (75%) during the first days but resolved spontaneously in all cases. In four cases, transient chest pain occurred, also quickly resolving within a few days after the procedure. At 1 to 6 months follow-up, 16 patients experienced a total of 14 COPD exacerbations, ranging from zero (N=4 patients) to three (N=1 patient) after 28 procedures. In this study, no life-threatening events occurred, and all adverse events could be managed with standard care. All adverse events are listed in table 3a and 3b.

Table 3a. Adverse events.

	number
Any course of prednisolone or antibiotics	
Treatment to 1 month of follow up	8
1 month to 6 months follow up after treatment	17
Respiratory adverse events from 1st and 2nd treatment to 1 month of follow up	
COPD exacerbation	6
Pneumonia	2
Pneumothorax	1
Slight hemoptysis <5 ml	21
Chestpain	4
H1N1 influenza	2
Cough	2
Respiratory adverse events from 1 to 6 months of follow up after completed treatment	
COPD exacerbation	14
Pneumonia	3
Pneumothorax	0
Slight hemoptysis <5 ml	0
Chestpain	2
H1N1 influenza	1
Cough	2
Pulmonary embolism (non treated lung)	1

Adverse events were scored for all 28 procedures performed in 16 patients.

Table 3b. Adverse events.

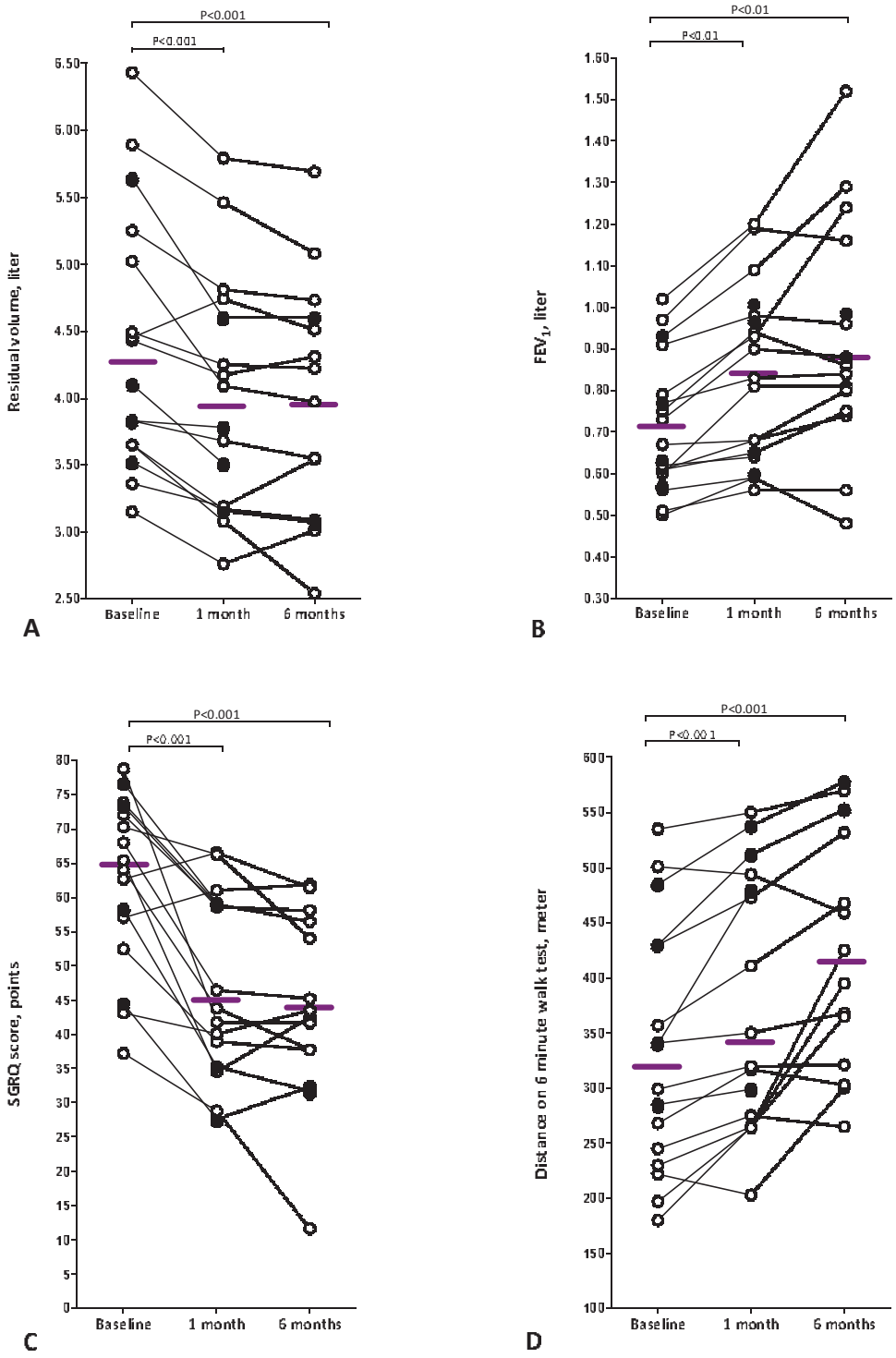
	number
Adverse events related to anaesthesia	
Paroxysmal atrial fibrillation	1
Phlebitis	1
Headache	2
Hoarseness	3
Bronchospasm	1
Adverse events, other causes	
Hypertension	1
Consolidation around LVR-coil	1
Nasal congestion	3
Tonsillar angina	1
Diarrhea	3
Oral candidiasis	3
Urinary tract infection	2
Traumatic rib contusion	1
Osteoporotic thoracic vertebral fracture	1
Gout	1
Wrist fracture	1
Azathioprine induced thrombopenia	1
Anemia	**1**

Adverse events were scored for all 28 procedures performed in 16 patients.

Efficacy

Compared with baseline, after 6 months, lung volume reduction coil treatment resulted overall in a significant improvement in SGRQ by 14.9±12.1 points, P <0.005), in FEV_1 by +14.9±17.0%, in forced vital capacity by +13.4±12.9%, in residual volume by -11.4±9.0%, and in distance on 6 minute walk test by +84.4±73.4 meter. Bilateral treatment further improved the initial single lung 1 month results. The initial responses observed in the pulmonary functions tests, distance on 6 minute walk test, and SGRQ, were sustained throughout the 6 month follow-up period (figure 5, table 4). More than 50% of the patients responded to above the minimal clinical important difference for FEV_1,[19] distance on 6 minute walk test,[20-22] and SGRQ[23] (table 5).

Figure 5. Individual results at baseline, 1 month after the first coil treatment, and 6 months after the last coil treatment.



Individual results at baseline, 1 month after the first coil treatment, and 6 months after the last coil treatment for patients who were treated bilaterally (○) and unilaterally (●). **A**. residual volume **B**. FEV_1 **C**. SGRQ total score **D**. distance on 6 minute walk test. The solid pink colored lines indicate the median values.

Table 4. Lung volume reduction coil treatment efficacy data.

	1 month of follow up post 1st treatment	1 month of follow up post 2nd treatment	3 months post 2nd treatment	6 months post 2nd treatment	6 months of follow up overall post treatments
	N=16	N=12	N=12	N=12	N=14
FVC, %	+11.5±13.6 (P=0.005)	+17.0±14.9 (P0.002)	+10.7±11.9 (P=0.010)	+13.3±13.2 (P=0.007)	+13.4±12.9 (P=0.002)
FEV_1, %	+10.3±13.1 (P=0.009)	+22.6±21.7 (P=0.004)	+19.9±20.0 (P=0.005)	+17.3±19.4 (P=0.010)	+14.9±17 (P=0.004)
RV, %	-9.5±6.5 (P<0.001)	-12.4±9.0 (P<0.001)	-11.1±9.9 (P=0.003)	-10.6±9.59 (P=0.004)	-11.4±9.0 (P<0.001)
Ratio of RV to TLC, %	-6.7±4.8 (P<0.001)	-8.2±7.1 (P=0.002)	-6.6±6.7 (P=0.006)	-8.1±5.2 (P<0.001)	-8.0±5.5 (P<0.001)
6MWD, meters	+35.4±30.6 (P<0.001)	+69.8±64.2 (P=0.003)	+62.2±76.6 (P=0.017)	+80.5±78.8 (P=0.005)	+84.4±73.4 (P<0.001)
6MWD, %	+12.6±13.8 (P=0.003)	+29.8±30.4 (P=0.006)	+27.1±36.6 (P=0.026)	+34.4±39.2 (P=0.011)	+32.9±36.3 (P=0.005)
SGRQ, points	-14.2±11.6 (P<0.001)	-12.2±13.5 (P=0.009)	-12.6±10.8 (P=0.002)	-15.8±12.2 (P=0.002)	-14.9±12.1 (P<0.001)

Data are presented as mean change from baseline ± standard deviation. FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 second, RV: residual volume; RV/TLC: ratio of residual volume to total lung capacity. 6MWD: distance on 6 minute walk test; SGRQ: St. George respiratory questionnaire.

Table 5. Responder rate at 6 month after lung volume reduction coil treatment using minimal clinically important difference.

	MCID	Responders	
Forced expiratory volume in 1 second	≥12%[19]	64%	N=9 of 14
Residual volume	≥10%	64%	N=9 of 14
Distance on 6 minute walk test	≥48 meter[20]	64%	N=9 of 14
Distance on 6 minute walk test	≥25 meter[21,22]	86%	N=12 of 14
St. George's respiratory questionnaire	≥4 points[23]	79%	N=11 of 14*

Responder rate given as the number of patients responding per total number of patients treated. MCID=minimal clinically important difference. * 11 of 14 patients improved by >14 points on the St. George's respiratory questionnaire.

DISCUSSION

For patients with advanced stage emphysema, there is a great need for medical treatments that can significantly improve quality of life, without inducing significant morbidity and mortality, and that are potentially available for the majority of patients. In this study, we showed the feasibility, safety, and efficacy of a new bronchoscopic lung volume reduction therapy by using segmentally inserted nitinol coils in patients with severe COPD, characterized by heterogeneous emphysema. From the first safety and feasibility report on the lung volume reduction coil treatment in 11 patients, using only three to six coils per lobe, we learned that patients with heterogeneous emphysema might benefit more than those with homogeneous emphysema.[11]

Therefore, in the current study, we report on patients number 12 to 27, who were treated using this technique with the following refinements: The lung volume reduction coil treatment was optimized by increasing the number of coils per lobe, a second generation coil was used, and the study focused entirely on patients with upper-lobe predominant heterogeneous emphysema. Heterogeneity was determined by a combination of subjective and objective assessments. First, the investigator assessed the sagittal reconstruction of the thin-slice CT scan to determine if there were focal regions of relatively high damage. Then, for cases that appeared to be heterogeneous, quantitative densitometry was used to determine the relative area of destruction (% of volume <-950 Hounsfield units) for both upper and lower lobes of the target lung. Besides lung tissue density quantification, the main role of the densitometry was to place an upper limit on tissue destruction in the treated lobe.

The uncontrolled, open-label design of this study can induce important placebo effects; however, we believe that significant improvements larger than the minimal clinically important difference for FEV_1, residual volume, and forced vital capacity, as well as for the distance on 6 minute walk test,[20-22] are not likely to be attributed to a placebo effect in these severely physically disabled patients. In two large (N=91 and N=98), uncontrolled, lung volume reduction device trials [24,25] in patients with severe upper lobe emphysema, no significant changes were observed in any pulmonary function test or in distance on 6 minute walk test despite bronchoscopic treatment.

In open-label, semi-invasive cohort studies like ours, patient reported outcomes such as the SGRQ can show marked placebo effects, and conclusions should be drawn with some caution. It is known from earlier uncontrolled trials,[8,24-26] for instance, that even without improvements in pulmonary function tests such as FEV_1, forced vital capacity, and residual volume, or exercise testing, the SGRQ improved significantly by more than the minimal clinically important difference[23] after bronchoscopic lung volume reduction. However, in our trial, the improvement was very large (mean improvement of 14.9 points compared with the SGRQ minimal clinically important difference of 4 points). Additionally, we found a close correlation between improvement in residual volume and improvement in SGRQ (eight of the nine patients with a clinically important difference in residual volume of greater than 10% also improved by more than 14 points on the SGRQ). A similarly close correlation was

also reported in a study with intrabronchial valves, in which the improvement in quality of life was associated with procedural efficacy as determined by loss of residual volume on a chest CT scan.[24]

Despite the fact that the lung volume reduction coil treatment was significantly enhanced from a median of five coils in our earlier first-in-human pilot study[11] to a median of 10 coils per lobe in this study, only one pneumothorax (<5%) was experienced, requiring, 48 hours of chest drainage, in 28 procedures using 260 coils. This rate is comparable to that in other bronchoscopic procedures with lung volume reduction devices.[7,24,27] Other adverse events observed that can be related to the actual lung volume reduction coil treatment were transient chest pain, possibly due to pleural traction of the coils, and very mild, transient hemoptysis. In the first month after lung volume reduction coil treatment we observed a relatively high number of exacerbations, related either to the bronchoscopy or to the actual placement of the coils. From previous bronchoscopic intervention trials, it is known that bronchoscopies by themselves induce COPD exacerbations.[28] But it is clear that placing 10 coils in the (sub-) segmental airways of one lobe can cause local airway mucosal damage, local edema, and bronchoconstriction, which may lead to a respiratory event. All events resolved with regular medical care, and no noninvasive ventilatory support or intensive care units admissions were required. After the first month, the frequency of exacerbations returned toward baseline levels.

We performed bilateral lung volume reduction coil treatments as sequential procedures for safety reasons. Early bronchoscopic lung volume reduction trials using one-way valves for total bilateral lobar occlusion reported a high rate of pneumothoraces when these bilateral treatments were performed in a single procedure.[29,30] On the other hand, in the bronchoscopic airway bypass procedure, in which up to 12 trans-bronchial stents were placed in both lungs in a single procedure, the pneumothorax rate remained very low.[28] One could argue that the LVR-coil procedure, in which total lobes are not occluded but only compressed, might be performed bilaterally in a single procedure, thereby significantly reducing the potential risks and costs of repeated bronchoscopy and anesthesia.[31]

Normally functioning lungs are elastic, efficiently expanding, and recoiling to drive air freely through the bronchi to the alveoli and back as the patient inhales and exhales. In the emphysematous lung, tissue is damaged and loses its elasticity.[32] The clinical and pulmonary function benefits seen after lung volume reduction coil treatment might be attributable to volume reduction, similar to the effects seen with lung volume reduction surgery,[33] by compressing diseased lung parenchyma due to the physical elastic properties of the nitinol wire of which the coils are made, and the improved mechanical properties of the remaining tissue that now expands following this compression.[34,35] To elicit these effects, the coils require some minimal amount of lung tissue to compress. Nitinol combines strength and memory shape properties with great elasticity, thereby improving tissue strength and elastic recoil, potentially further reducing the dynamic hyperinflation that occurs easily in these patients.[34,35]

There are currently a number of bronchoscopic lung volume reduction treatments for emphysema under clinical investigation. The available endobronchial one-way valves, designed for segmental and lobar airway closure, only work when there is no, or only very limited, collateral ventilation.[9,24,36] Although these devices work well in patients without collateral ventilation, the low responder rate of these treatments in randomly selected heterogeneous patients clearly shows the need for an intervention that works independently of collateral flow, which is significant in a large proportion of patients with severe emphysema.[36,37] Although the current study reports the results on a small sample, we have already observed a very encouraging responder rate. However, because this was an open-label cohort pilot study, one of the next steps should be to confirm the results in a larger randomized controlled trial, using a more specific definition of heterogeneity as an inclusion criterion. Furthermore, we think that future studies on lung volume reduction coil treatment are warranted in a wider range of emphysema phenotypes such as homogeneous disease.

CONCLUSION

Lung volume reduction coil treatment is a promising novel bronchoscopic technique for the treatment of patients with severe heterogeneous emphysema. The lung volume reduction coil treatment works independently of collateral flow and showed a high responder rate in this early phase clinical trial. The lung volume reduction coil procedure is technically feasible and results in significant improvements in pulmonary function, exercise capacity, and quality of life, with an acceptable safety profile.

Acknowledgments

The authors thank Alie Smidt, from the University Medical Center Groningen Endoscopy Center for her skillful support during all bronchoscopies performed, and the University Medical Center Groningen pulmonary function department for their dedicated testing.

REFERENCES

1. Rabe KF, Hurd S, Anzueto A, et al; Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2007; 176 (6): 532-555.

2. O'Donnell DE, Webb KA. The major limitation to exercise performance in COPD is dynamic hyperinflation. J Appl Physiol. 2008; 105 (2): 753-755.

3. Casanova C, Cote C, de Torres JP, et al. Inspiratory-to-total lung capacity ratio predicts mortality in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2005; 171 (6): 591-597.

4. Martinez FJ, Chang A. Surgical therapy for chronic obstructive pulmonary disease. Semin Respir Crit Care Med. 2005; 26 (2): 167-191.

5. 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(21): 2059-2073.

6. Hosenpud JD, Bennett LE, Keck BM, et al. Effect of diagnosis on survival benefit of lung transplantation for end-stage lung disease. Lancet. 1998; 351 (9095): 24-27.

7. Hopkinson NS, Toma TP, Hansell DM, et al. Effect of bronchoscopic lung volume reduction on dynamic hyperinflation and exercise in emphysema. Am J Respir Crit Care Med. 2005; 171 (5): 453-460.

8. Wood DE, McKenna RJ Jr, Yusen RD, et al. A multicenter trial of an intrabronchial valve for treatment of severe emphysema. J Thorac Cardiovasc Surg. 2007; 133 (1): 65 – 73.

9. 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(13): 1233-1244.

10. Gompelmann D, Eberhardt R, Michaud G, Eet al. Predicting atelectasis by assessment of collateral ventilation prior to endobronchial lung volume reduction: a feasibility study. Respiration. 2010; 80 (5): 419-425.

11. Herth FJ, Eberhard R, Gompelmann D, Slebos DJ, Ernst A. Bronchoscopic lung volume reduction with a dedicated coil: a clinical pilot study. Ther Adv Respir Dis 2010;4(4)225-231.

12. American Thoracic Society. Surveillance for respiratory hazards in the occupational setting. Am Rev Respir Dis. 1982; 126 (5): 952-956.

13. Stoel BC, Bode F, Rames A, Soliman S, Reiber JH, Stolk J. Quality control in longitudinal studies with computed tomographic densitometry of the lungs. Proc Am Thorac Soc. 2008;5 (9): 929-933.

14. Stolk J, Versteegh MI, Montenij LJ, et al. Densitometry for assessment of effect of lung volume reduction surgery for emphysema. Eur Respir J. 2007; 29 (6): 1138 – 1143.

15. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A selfcomplete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire.
Am Rev Respir Dis. 1992; 145 (6): 1321-1327.

16. Miller MR, Crapo R, Hankinson J, et al; ATS/ERS Task Force. General considerations for lung function testing. Eur Respir J. 2005; 26 (1): 153-161.

17. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166 (1): 111-117

18. Nomenclature of broncho-pulmonary anatomy; an international nomenclature accepted by the Thoracic Society. Thorax. 1950; 5 (3): 222 – 228.

19. Donohue JF. Minimal clinically important differences in COPD lung function. COPD. 2005; 2 (1): 111-124.

20. Wise RA, Brown CD. Minimal clinically important differences in the six-minute walk test and the incremental shuttle walking test. COPD. 2005; 2 (1): 125-129.

21. Puhan MA, Chandra D, Mosenifar Z, et al; National Emphysema Treatment Trial (NETT) Research Group. The minimal important difference of exercise tests in severe COPD. Eur Respir J. 2011; 37 (4): 784-790.

22. Holland AE, Hill CJ, Rasekaba T, et al. Updating the minimal important difference for six-minute walk distance in patients with chronic obstructive pulmonary disease.
Arch Phys Med Rehabil. 2010; 91 (2): 221-225.

23. Jones PW. St. George's Respiratory Questionnaire: MCID. COPD. 2005; 2 (1): 75-79.

24. Sterman DH, Mehta AC, Wood DE, et al; IBV Valve US Pilot Trial Research Team. A multicenter pilot study of a bronchial valve for the treatment of severe emphysema. Respiration 2010; 79 (3): 222-233.

25. Springmeyer SC, Bolliger CT, Waddell TK, Gonzalez X, Wood DE; IBV Valve Pilot Trials Research Teams. Treatment of heterogeneous emphysema using the spiration IBV valves.
Thorac Surg Clin. 2009; 19 (2): 247-253.

26. Snell GI, Hopkins P, Westall G, et al. A feasibility and safety study of bronchoscopic thermal vapor ablation: a novel emphysema therapy. Ann Thorac Surg. 2009; 88 (6): 1993-1998.

27. Wan IY, Toma TP, Geddes DM, et al. Bronchoscopic lung volume reduction for end-stage emphysema: report on the first 98 patients. Chest. 2006; 129 (3): 518-526.

28. Cardoso PF, Snell GI, Hopkins P, et al. Clinical application of airway bypass with paclitaxel-eluting stents: early results. J Thorac Cardiovasc Surg. 2007; 134 (4): 974-981.

29. Venuta F, de Giacomo T, Rendina EA, et al. Bronchoscopic lung-volume reduction with one-way valves in patients with heterogeneous emphysema. Ann Thorac Surg. 2005; 79(2): 411-416.

30. Yim AP, Hwong TM, Lee TW, et al. Early results of endoscopic lung volume reduction for emphysema. J Thorac Cardiovasc Surg. 2004; 127 (6): 1564-1573.

31. Edrich T, Sadovnikoff N. Anesthesia for patients with severe chronic obstructive pulmonary disease. Curr Opin Anaesthesiol. 2010; 23 (1): 18-24.

32. Cooper CB. The connection between chronic obstructive pulmonary disease symptoms and hyperinflation and its impact on exercise and function. Am J Med. 2006; 119(10)(suppl 1): 21-31.

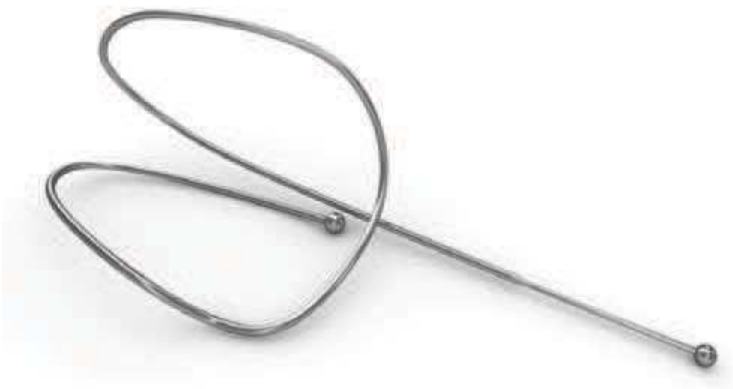
33. Sciurba FC, Rogers RM, Keenan RJ, et al. Improvement in pulmonary function and elastic recoil after lung-reduction surgery for diffuse emphysema. N Engl J Med. 1996; 334(17):1095-1099.

34. Shabalovskaya SA. Surface, corrosion and biocompatibility aspects of Nitinol as an implant material. Biomed Mater Eng. 2002; 12 (1): 69-109.

35. Duerig TW, Pelton AR, Stöckel D. The utility of superelasticity in medicine. Biomed Mater Eng. 1996; 6 (4): 255-266.

36. Fessler HE. Collateral ventilation, the bane of bronchoscopic volume reduction. Am J Respir Crit Care Med. 2005; 171 (5): 423-424.

37. Hogg JC, Macklem PT, Thurlbeck WM. The resistance of collateral channels in excised human lungs. J Clin Invest. 1969;48 (3): 421-431.



CHAPTER

8

Lung volume reduction coil treatment for patients with severe emphysema: a European multicenter trial

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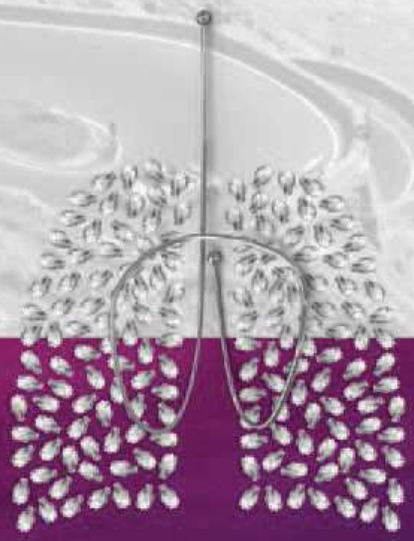


Adapted from

Thorax 2014;69:980-6.

Key messages

What is the key question?
Is lung volume reduction coil treatment feasible and does it sustainably improve quality of life and clinical outcomes in a broad group of patients with severe emphysema treated in a multicenter setting?

What is the bottom line?
Bronchoscopic lung volume reduction coil treatment is associated with a good safety profile and significantly improves quality of life, exercise capacity and pulmonary function in abroad group of patients with severe emphysema, with sustained results at 1 year.

Why read on?
Further post hoc analysis of CT scan heterogeneity showed significant responses in both heterogeneous and homogeneous emphysema, suggesting that lung volume reduction coil treatment may benefit patients with both heterogeneous and homogeneous emphysema disease distribution.

ABSTRACT

Background
The lung volume reduction coil is a minimally invasive bronchoscopic nitinol device designed to reduce hyperinflation and improve elastic recoil in severe emphysema. We investigated the feasibility, safety and efficacy of lung volume reduction coil treatment in a prospective multicenter cohort trial in patients with severe emphysema.

Methods
Patients were treated in 11 centers. Safety was evaluated by recording all adverse events, efficacy by the St. George's Respiratory Questionnaire (SGRQ) as primary endpoint, and pulmonary function testing, modified Medical Research Council dyspnea score (mMRC) and distance on the 6 minute walk test up to 12 months after the final treatment.

Results
Sixty patients (60.9±7.5 years, forced expiratory volume in 1 second (FEV_1) 30.2±6.3% predicted) were bronchoscopically treated with coils (55 bilateral, 5 unilateral), with a median of 10 (range 5–15) coils per lobe.

Within 30 days post lung volume reduction coil treatment, 7 COPD exacerbations (6%), 6 pneumonias (5%), 4 pneumothoraces (4%) and 1 hemoptysis (1%) occurred as serious adverse events.

At 6 and 12 months, respectively, change in SGRQ was −12.1±12.9 points and −11.1±13.3 points, change in distance on 6 minute walk test was +29.7±74.1 meter and +51.4±76 meter, change in FEV_1 was +0.11±0.20 Liter and +0.11±0.30 Liter, and change in residual volume was −0.65±0.90 Liter and −0.71±0.81 Liter (all $P<0.01$).

Post-hoc analyses showed significant improvements in SGRQ, distance on 6 minute walk test and residual volume in patients with both heterogeneous and homogeneous emphysema.

Conclusion
Lung volume reduction coil treatment results in significant clinical improvements in patients with severe emphysema, with a good safety profile and sustained results for up to 1 year.

INTRODUCTION

For patients with advanced chronic obstructive pulmonary disease (COPD) who, despite optimal medical management still have severe dyspnea, bronchoscopic lung volume reduction could be a beneficial treatment option.[1,2] Although lung volume reduction surgery and lung transplantation are still valid treatment modalities for patients with COPD, the use of these interventions is very limited because of strict patient selection criteria, significant morbidity and donor shortage.[3–5]

To date, bronchoscopic lung volume reduction using one-way endobronchial valves has been the most extensively investigated technique in this field.[6–8] However, successful clinical outcomes from endobronchial valve treatment can only be achieved in patients with no interlobar collateral ventilation and when the one-way valves are placed to entirely block all the airways into the target lobe, which can be technically difficult due to local anatomy and in the absence of significant experience with these devices.[6–8] It is estimated that only about 33% of patients with severe emphysema have no collateral ventilation between the target and adjacent lobe and can thus potentially be treated using one-way valves.[1] This clearly shows the need for alternative bronchoscopic treatments that work independently of the presence of collateral ventilation.

In 2010 we reported the first human trial using bronchoscopically delivered nitinol lung volume reduction coils.[9] Up to six shape-memory coils per lung were placed in patients with severe emphysema, resulting in moderate effects only in the patients with heterogeneous emphysema but without any serious adverse events. After that first trial we improved the lung volume reduction coil treatment to target the most diseased areas of the lung with approximately 10 coils placed per lobe, in order to maximize re-tensioning of the airway network. The results using this approach in 16 patients with upper lobe predominant heterogeneous emphysema have previously been published, showing feasibility and safety and also demonstrating statistically and clinically significant improvements in pulmonary function, exercise capacity and quality of life.[10] Surprisingly, even in this early pilot phase, two-thirds of the patients treated responded beyond the minimal clinically important differences for forced expiratory volume in 1 second (FEV_1),[11] residual volume (RV),[12] distance on 6 minute walk test (6MWD)[13] and St. George's Respiratory Questionnaire (SGRQ).[14]

Following the successful early experiences in these two pilot trials, the current study allowed further investigation into the feasibility, safety and efficacy of lung volume reduction coil treatment in a multicenter setting in a larger group of patients.

METHODS

This prospective open-label multicenter feasibility study was conducted in 11 hospitals in France, Germany and the Netherlands and was approved by the ethics committee at each site. The first patient was enrolled in December 2009 and the final patient in October 2011. The initial protocol proposed a follow-up period of 6 months following initial treatment. However, because the Dutch and French ethics committees required a 12 month follow-up period, the protocol was modified to require a 12 month follow-up for patients in the Netherlands and France, while maintaining the original 6 month follow-up period for patients in Germany. This paper reports on all patients in the study at both exit points.

Patients

Patients with COPD with upper or lower lobe predominant bilateral heterogeneous emphysema on chest CT scan as judged by the treating physician were considered for inclusion. All patients were intended to be treated bilaterally, in accordance with the protocol assessment schedule. The study inclusion and exclusion criteria are presented in box 1.

Box 1. Study inclusion and exclusion criteria.

Main inclusion criteria

- >35 years of age
- CT scan indicates bilateral heterogeneous emphysema
- Post-bronchodilator FEV_1 <45% of predicted
- Total lung capacity >100% of predicted
- Residual volume >175% of predicted
- mMRC >2 (0–4)
- Stopped smoking for >8 weeks prior to entering the study

Main exclusion criteria

- Change in FEV_1 >20% post-bronchodilator
- Carbon monoxide diffusing capacity <20% of predicted
- History of recurrent clinically significant respiratory infection
- Pulmonary hypertension: right ventricular pressure >50 mmHg
- Inability to walk >140 meter in 6 minutes
- Previous lung volume reduction surgery, lung transplant or lobectomy
- Clinically significant bronchiectasis
- Giant bullae more than one-third lung volume
- Severe destructed homogeneous emphysema by CT scan
- Patient on antiplatelet agent or anticoagulant therapy or has not been weaned off prior to procedure

Lung volume reduction coil treatment

Lung volume reduction coil treatment was performed as previously described.[10] Briefly, the RePneu lung volume reduction coil (PneumRx, USA) (figure 1) is an implantable device composed of preformed nitinol wire which is straightened for delivery via a therapeutic flexible bronchoscope into sub-segmental airways using a special delivery catheter, cartridge and loading forceps. Once in place, it is released and recovers to a non-straight predetermined shape upon deployment. Seven sizes of coil were available (70, 85, 100, 125, 150, 175 and 200 mm). All procedures were performed under general anesthesia and the deployment of the coil was visualized under fluoroscopy. The coils were deployed with the objective of achieving equal sub-segmental distribution throughout one target lobe. The contralateral procedure was performed at least 1 month after the first procedure.

Figure 1. Fully deployed nitinol lung volume reduction coils (150, 125 and 100 mm).

Assessments and follow-up

Screening assessments included medical history, physical examination, dyspnea assessment by the modified Medical Research Council dyspnea scale (mMRC), quality of life assessment by the SGRQ,[15] echocardiogram, pre- and post-bronchodilator spirometry, lung volume measurements by body plethysmography,[16] 6 minute walk test,[17] chest X-ray and a thoracic CT scan. The patient was kept at least overnight after the procedure. A 1 month follow-up evaluation was performed, after which the second procedure was scheduled. Patients were then followed at 1, 3, 6 and 12 months (the latter only in France and The Netherlands).

Primary & secondary endpoints and Safety objectives

The primary efficacy endpoint was the improvement in SGRQ total score from baseline compared with the score at 6 months. The secondary efficacy endpoints were the comparison between baseline and 6 months for forced vital capacity (FVC), FEV_1, residual volume, ratio of residual volume to total lung capacity (RV/TLC), improvement in distance on 6 minute walk test and mMRC score. The responder rate at 6 months was calculated using the minimal clinically important difference defined for FEV_1,[11] RV,[12] 6MWD[13] and SGRQ.[14] The safety objectives were to identify the number and type of device-related and procedure related adverse events related to the use of the LVR-coil.

Post-hoc CT scan analyses

Since inclusion in this trial was based on the treating physicians' visual chest CT judgment, a post-hoc analysis was performed on these CT scans to analyze the relationships between the response to lung volume reduction coil treatment at 12 months follow-up and the level of heterogeneity assessed by a blinded qualitative visual 4-point tissue destruction score scale (0–25%, 26–50%, 51–75%, >75% visible tissue destruction), as well as by calculating the percentage area of destruction below −950 Hounsfield units between the upper and lower lobes of both lungs. Quantitative CT analyses were blinded and performed with CIRRUS Lung 13.10 (Diagnostic Image Analysis Group Nijmegen, The Netherlands; Fraunhofer MEVIS, Bremen, Germany). The lungs and lobes were automatically segmented and visually inspected. Emphysema was quantified per lobe as an emphysema score: the percentage of voxels below −950 Hounsfield units.[18] For the visual assessment, a patient was classified as heterogeneous if there was a difference of more than 1 point between ipsilateral lobes on both sides. For the computerized assessment, a patient was classified as heterogeneous when the difference for both lungs in the lung tissue destruction score was >25% at −950 Hounsfield units between ipsilateral upper and lower lobes.

Statistics

This trial was powered on the statistical significant difference in expected SGRQ total score between baseline and the 6 month follow-up time point using an $\alpha<0.05$ with a power of 0.90, taking a patient loss to follow-up of 10% into account.[10]

Data are presented as mean ± standard deviation, except for the presentation of the five unilateral cases and descriptive statistics on the detailed procedural results (table 2) where data are expressed as median (minimum−maximum) or mean ± standard deviation when appropriate. The statistical significance of changes from baseline was assessed by the paired student t-test. A linear regression analysis was performed to associate outcome at 6 months for changes in SGRQ and distance on 6 minute walk test, using as baseline regressors residual volume % of predicted value, ratio of residual volume to total lung capacity, FEV_1 % of predicted value, forced vital capacity, age, carbon monoxide lung transfer factor and emphysema type (homogeneous or heterogeneous disease). The models were simple linear with no interactions or terms higher than first order included; $P<0.05$ was considered statistically significant. SAS version 9.3 was used for all analyses. All data in this trial were independently monitored by a contract research organization.

RESULTS

Patients and procedures

Sixty patients were enrolled between December 2009 and October 2011 and their baseline demographics are shown in table 1. A total of 115 procedures were performed (5 patients had unilateral treatment, figure 2; study flow chart) in which a total of 1125 coils were placed. A median of 10 coils (range 5–15) was placed per lobe (table 2).

Table 1. Patient demographics and baseline characteristics (N=60).

Characteristics	Outcome
Female/Male	33/27
Age, years	60.9±7.5
Pack-years	39.5±18.2
BMI, kg/m^2	25±4
FEV_1, Liter	0.83±0.25
FEV_1, % of predicted value	30±6
FVC, Liter	2.49±0.78
FVC, % of predicted value	74±17
Ratio of FEV_1 to FVC, %	34±7
RV, Liter	5.29±1.32
RV, % of predicted value	249±53
Ratio of RV to TLC, %	66±8
Distance on 6 minute walk test, meter	316±102
SGRQ, points	62±14
Supplemental Oxygen, N (%)	35 (58%)
mMRC, points	3.0±0.75

Data are shown as mean ± standard deviation. BMI, body mass index; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; mMRC, modified Medical Research Council dyspnea score; RV, residual volume; TLC, total lung capacity; SGRQ, St George's Respiratory Questionnaire total score.

Figure 2. Study flow chart.

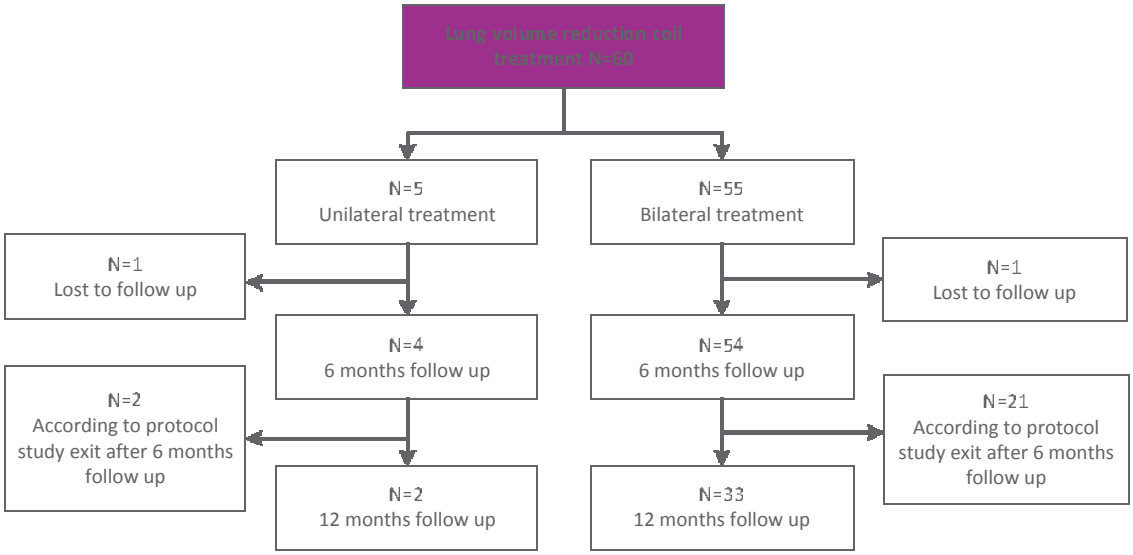


Table 2. Bronchoscopic lung volume reduction coil procedure results.

	Outcome
Number of procedures	115
Procedure time, minutes	
Mean	49.9±23.2
Median	45.0 (20-135)
Post-procedure hospital stay, days	
Mean	2.3±2.8
Median	1.0 (0-19)
Coils per procedure, number	
Mean	9.8±1.4
Median	10 (5-15)
Total coils implanted	1125
Upper, right Lobe	437
Upper, left Lobe	450
Lower, right Lobe	110
Lower, left Lobe	121
Middle, right Lobe	7
Coil implant Size	
70 mm	5
85 mm	20
100 mm	508
125 mm	462
150 mm	101
175 mm	28
200 mm	1

Data are shown as numbers, mean ± standard deviation, or median (minimum-maximum).

Safety

No periprocedural serious adverse events occurred in the 115 bronchoscopies performed under general anesthesia. No death or respiratory failure was reported. A summary of all serious and non-serious respiratory adverse events is listed in table 3. All events were treated and resolved with routine medical care and without sequelae.

Table 3. Adverse events.

	Treatment – 1 month		**> 1 month - 6 months**		**> 6 months - 12months**	
	events	patients	**events**	patients	**events**	patients
Serious respiratory adverse events						
COPD exacerbation	**7**	7	**12**	10	**4**	3
Pneumonia	**6**	5	**3**	3	**6**	6
Haemoptysis	**1**	1	**0**	0	**0**	0
Pneumothorax	**4**	4	**2**	2	**1**	1
Respiratory adverse events						
COPD exacerbation	**8**	7	**21**	15	**19**	15
Pneumonia	**5**	3	**4**	3	**3**	3
Mild haemoptysis (<5mL)	**61**	35	**3**	3	**2**	2
Cough	**2**	2	**3**	3	**0**	0
Transient chest pain	**28**	20	**7**	6	**3**	3

Adverse events presented per procedure for the first month after each procedure (115 procedures in total), for patients in the 1–6 month follow-up period (N=58) and for patients in the 6–12 month follow-up period (N=35). Events reported for both unilateral and bilateral treated patients.

Efficacy all patients

Of the 60 patients who were treated, 58 patients were evaluable at 6 months and 35 patients at 12 months (23 patients from Germany exited the study at 6 months). Because the German cohort exited the study at 6 months, we segregated the data to compare patients with 1-year follow-up data against their own 6 month results to analyze the sustainability of the clinical improvements within the same population (table 4). Across key clinical parameters, FEV_1 % predicted, residual volume % predicted and SGRQ results were sustained while mean distance on 6 minute walk test actually improved between 6 and 12 months. The minimal clinically important difference responder percentages for FEV_1, residual volume, distance on 6 minute walk test and SGRQ are shown in table 5.

Efficacy unilateral patients

Five patients were treated unilaterally. The reasons for treating only one lung were: lost to follow-up in two patients; second lung on second look not suitable for treatment (bullae) in one patient; and second lung declined by two patients (one improved satisfactory and one did not want to proceed with the trial). At 6 month follow-up in four evaluable patients, the median change in FEV_1 was +4.7% (range −17.8 to +17.0%), median change in distance on 6 minute walk test was +29 meter (range −46 to +92 meter) and residual volume and ratio of residual volume to total lung capacity remained stable.

Heterogeneous versus homogeneous disease

In the 33 bilaterally treated patients with 12 months follow-up, the post-hoc visual qualitative CT score of the degree of tissue destruction classified 20 patients as heterogeneous and 13 as homogeneous. When using the CT software analysis, 16 patients were classified as heterogeneous and 17 as homogeneous. Regardless of the classification method, both heterogeneous and homogeneous patients showed significant improvement at 1 year follow-up (table 6).

Upper versus lower lobe disease

In this trial lower lobe treatment was performed in 10 patients, of whom nine could be evaluated at the 6 month endpoint. Except for FEV_1 (+0.04±0.08 Liter for lower lobe versus +0.15±0.23 Liter for upper lobe; P=0.026), there were no statistically significant differences in the clinical responses between patients with upper versus lower lobe disease for residual volume, distance on 6 minute walk test and SGRQ.

Responder analysis

To identify lung volume reduction coil treatment responders we performed a multivariable analysis for the primary endpoint SGRQ and for the distance on 6 minute walk test. None of the input regressors (residual volume % of predicted value, ratio of residual volume to total lung capacity, FEV_1 % of predicted value, forced vital capacity, age, carbon monoxide lung transfer factor and emphysema type) were useful in associating patient outcomes at 6 months follow-up.

Table 4. Efficacy results at 6 months and 12 months of follow-up.

	Overall group (N=58) at 6 months of follow up	12 months FU group (N=34) at 6 months of follow up	12 months FU group (N=34) at 12 months of follow up
FEV_1, Liter	+0.11±0.20 (N=54, P<0.001)	+0.12±0.28 (N=33, P=0.021)	+0.11±0.30 (N=34, P=0.037)
FEV_1, %	+15±27 (N=54, P<0.001)	+18±32 (N=33, P=0.003)	+16±36 (N=34, P=0.017)
FVC, Liter	+0.20±0.53 (N=54, P=0.008)	+0.33±0.57 (N=33, P=0.0020	+0.28±0.45 (N=34, P=0.001)
RV, Liter	-0.65±0.90 (N=58, P<0.001)	-0.80±1.03 (N=34, p<0.001)	-0.71±0.81 (N=34, P<0.001)
RV, %	-11±15 (N=58, P<0.001)	-14±15 (N=34, P<0.001)	-14±13 (N=34, P<0.001)
Ratio of RV to TLC, %	-5±12 (N=58, P<0.007)	-6±9 (N=34, P<0.001)	-3±19 (N=34, P=0.245)
Distance on 6 minute walk test, meter	+30±74 (N=56, P=0.004)	+42±74 (N=34, P=0.002)	+51±76 (N=32, P=0.003)
SGRQ, points	-12±13 (N=56, P<0.001)	-10±16 (N=33, P<0.001)	-11±13 (N=32, P<0.001)
mMRC, points	-0.6±1.2 (N=58, P<0.001)	-0.8±0.9 (N=34, P<0.001)	-0.7±0.8 (N=34, P<0.001)

Efficacy at 6 months for all lung volume reduction coil treatments (N=58, overall group) and at 6 and 12 months (N=34, 12 month follow-up group columns). Results are given as change from baseline. Data are shown as mean ± standard deviation. Data in parentheses are the numbers of actual measurements available per variable tested followed by the actual P value. FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; mMRC, modified Medical Research Council dyspnea score; RV, residual volume; SGRQ, St George's Respiratory Questionnaire total score; TLC, total lung capacity.

Table 5. Responder rates at 6 months and 12 months.

	MCID	6 months	12 months
Forced expiratory volume in 1 second	**≥ 12%[11]**	48%	41%
Residual volume	**≥ 0.35[12]**	65%	58%
Distance on 6 minute walk test	**≥ 26 meter[13]**	53%	60%
St. George's respiratory questionnaire	**≥ 4 points[14]**	74%	66%
St. George's respiratory questionnaire	**≥ 8 points**	61%	53%

Responder rates at 6 and 12 months after bilateral lung volume reduction coil treatment using minimal clinically important differences (MCID). Results are given as percentage of responders to total patients.

Table 6. Results at 12 months after bilateral lung volume reduction coil treatment for patients classified as heterogeneous and homogeneous emphysema.

	Visual CT assessment at 12 months of follow up		
	Heterogeneous (N=20)	**Homogeneous (N=13)**	**P value**
FEV_1, Liter	+0.14±0.30	+0.08±0.28	ns
Residual volume, Liter	-0.69±0.87	-0.68±0.46	ns
Distance on 6 minute walk test, meter	+54±65	+46±68	ns
SGRQ, points	-13±15	-7±9	ns

	Digital CT assessment at 12 months of follow up		
	Heterogeneous (N=16)	**Homogeneous (N=17)**	**P value**
FEV_1, Liter	+0.18±0.32	+0.05±0.26	ns
Residual volume, Liter	-0.75±0.78	-0.66±0.72	ns
Distance on 6 minute walk test, meter	+75±67	+28±58	0.05
SGRQ, points	-12±14	-9±13	ns

Results are given as mean ± standard deviation in change from baseline. Heterogeneity and homogeneity were assessed by both a visual CT assessment (a 4-point qualitative score of the degree of tissue destruction where a difference of ≤1 point for both lungs was regarded as homogeneous) and a digital CT assessment (where the software calculated the percentage area of destruction at –950 Hounsfield units; a difference of ≤25% in destruction for both lungs was regarded as homogeneous). *P<0.05 for all end-points compared to baseline.

DISCUSSION

This prospective multicenter study assessed the long-term safety and improvements in patient-related outcome measures of lung volume reduction coil treatment in 60 patients with severe emphysema. The results show an acceptable safety profile associated with a significant and sustained improvement over 12 months in relevant clinical and functional parameters including FEV_1, residual volume, distance on 6 minute walk test and SGRQ.

This is the largest lung volume reduction coil study to date, and also evaluated longer-term results of lung volume reduction coil treatment. In our first pilot study (N=16) using the current treatment approach (median 10 coils per lung) and coil design, significant clinical and functional improvements were seen at 6 months including SGRQ (−14.9 points), FEV_1 (+14.9%), residual volume (−11.4%) and distance on 6 minute walk test (+84 meter) with an acceptable safety profile.[10] Recently, Shah et al[19] reported the results at 90 days after bilateral lung volume reduction coil treatment for 46 patients included in a randomized controlled study and demonstrated a significant improvement in SGRQ (−8.1 points), FEV_1 (+14%), residual volume (−0.51 Liter) and distance on 6 minute walk test (+51 meter), with no difference in serious adverse events between treatment and control groups.

In the present multicenter study involving 11 centers, no serious adverse events were reported during the lung volume reduction coil treatment procedures, demonstrating procedural safety. Serious adverse events (table 3) mainly occurred in the 30 days after the procedure, with all events resolving with regular medical care and without sequelae. Our results confirm the acceptable safety profile for lung volume reduction coil treatment with a rate of adverse events similar to previous reports on lung volume reduction coil treatment.[10,19] The rate of post-procedure exacerbations and pneumonia is comparable to reported events with endobronchial one-way valves.[6,8] Importantly, the total rate of these COPD-related events following endoscopic implants did not exceed the number of exacerbations and pneumonia that were reported in the EASE trial sham bronchoscopy control group.[20] Lung volume reduction coil specific procedure-induced events that occur are typically very mild hemoptysis or colored sputum requiring no intervention in about 50% of subjects and temporary chest discomfort for a few days requiring either a standard painkiller regimen for a few days or no intervention at all in about one-third of subjects treated.

Regarding efficacy, our results show significant improvements in clinical and functional parameters at 6 months with a magnitude of response in line with the two recent reports on lung volume reduction coil treatment,[10,19] reporting on 6 month and 3 month follow-up, respectively. Our study provides the first longer-term analysis of data over 12 months after bilateral lung volume reduction coil treatment and demonstrates a sustained response at 12 months. To better analyze the relevance of the efficacy results, we analyzed the minimal clinically important difference in FEV_1,[11] residual volume,[12] distance on 6 minute walk test,[13] and SGRQ[14] and found a significant responder rate at 6 and 12 months for these clinical endpoints (table 5).

The cohort trial design can, of course, induce bias. However, the results reported are higher than reported minimal clinically important difference for our endpoints and show similar efficacy across multiple centers. Furthermore, we have previously shown that, even in a sham controlled bronchoscopic interventional trial design, no real placebo effect could be observed in patients with severe COPD.[20]

To better understand the predictors of response to lung volume reduction coil treatment, we conducted a multivariate analysis to assess the relationship between the response to treatment and baseline variables typically identified as predictors of outcome, such as hyperinflation and emphysema heterogeneity. Using the 6 month endpoints, none of the evaluated baseline variables provided a meaningful predictor of response to lung volume reduction coil treatment. Other potential variables could include nuanced emphysema phenotypes beyond heterogeneous or homogeneous classification, such as more or less small airways disease, centrilobular versus panlobular emphysema and variability in placement strategies including proximal versus distal placement within the sub-segmental airways and/or the number and size of coils deployed. The current active clinical trials (NCT01822795[21] and NCT01608490) and future meta-analysis data of patients treated in the four European clinical studies thus far may increase the statistical power sufficiently to perform this analysis better. In our study, where broad selection criteria were purposely used in order to evaluate the effectiveness in a population of patients representative of the patients we see in daily practice, we found a large variability of response between patients. However, responder rates overall for several endpoints were already high (table 5). The difficulty of identifying strong predictors of success has been previously demonstrated by a predictive multivariate effort completed in a much larger patient cohort (N=608) for outcome after lung volume reduction surgery. In this large group, only a very weak signal for the ratio of residual volume to total lung capacity and emphysema distribution could be demonstrated.[22]

Lung hyperinflation is a major feature of emphysema and is associated with dyspnea, exercise intolerance and compromised daily physical activity.[23,24] In this study, neither baseline residual volume nor the ratio of residual volume to total lung capacity as % of predicted value the response to lung volume reduction coil treatment. This is possibly due to the fact that residual volume greater than 175% of predicted value was an inclusion criterion, resulting in treatment of severe static hyperinflated patients (mean baseline residual volume 249±53% of predicted value). On the other hand, the magnitude of change in residual volume after lung volume reduction coil treatment was associated with more favorable mean clinical and functional outcomes in this study, suggesting that residual volume changes may be viewed as a marker of response to treatment and that, by selecting patients with more potential for significant residual volume decrease, the likelihood of significant clinical benefit may be increased. The finding that residual volume is reduced by lung volume reduction coil treatment might be related to mechanical volume compression of lung tissue exerted by the coils, as well as improvement in elastic recoil achieved by decreasing airway resistance.[25]

When comparing the results for patients with upper lobe versus lower lobe treatment, no outcome differences were observed for residual volume, distance on 6 minute walk test

and SGRQ. The lower FEV_1 results seen with lower lobe coil treatments is comparable to the experience with lung volume reduction surgery in the lower lobes where the effect on improving FEV_1 is also limited compared with other outcome variables.[26] However, because FEV_1 in general shows poor correlation with performance in patients with severe emphysema,[27] and that patient-relevant outcomes such as distance on 6 minute walk test and SGRQ show strong improvement even in lower lobe subjects, lower lobe treatment with coils appears to be a clinically valid treatment option with clear patient benefit. Future work will evaluate whether, as currently hypothesized, the much bigger lower lobes require a greater number of coils to optimize results.

Our post-hoc CT analysis showed that a large number of patients were classified as homogeneous when using both a visual and a digital assessment, even though the inclusion criteria called for heterogeneous patients per clinicians' visual assessment. This finding should be cautiously considered, since this trial was not designed to prospectively identify homogeneous emphysema patients and the two methods of creating a heterogeneous versus a homogeneous group are arbitrary. Our results show that lung volume reduction coil treatment also benefits patients with less pronounced heterogeneous to homogeneous disease. Our data showed a statistically and clinically significant benefit for both groups compared with baseline, with overall a potentially increased mean efficacy for the heterogeneous patient group. The fact that lung volume reduction coil treatment also shows efficacy in patients with homogeneous emphysema is a very important finding, challenging the assumption that only patients with heterogeneous emphysema will respond to lung volume reduction coil treatment, as has been shown for surgical lung volume reduction[28] and endobronchial valve treatment.[6,7] Of note, other bronchoscopic techniques such as thermal vapor ablation[29] and sealant therapy[30] are also restricted to upper lobe predominant heterogeneous emphysema, leaving a broad group of patients with non-upper lobe predominant and homogeneous disease without a treatment option. It can be hypothesized that lung volume reduction coil treatment is similarly efficient in both heterogeneous and homogeneous emphysema because of a different mechanism of action from true 'lung volume reducing' therapies, as the primary mechanism of action of coils appears to be mechanical re-tensioning of the airway network rather than just reducing absolute lung volume alone. However, additional studies are necessary to better characterize the mechanisms of action of coils and also to confirm the efficacy of lung volume reduction coil treatment in homogeneous emphysema, which represents a large number of patients usually excluded from other surgical and bronchoscopic lung volume reduction treatment options.

CONCLUSION

This study provides multicenter evidence for the feasibility, procedural safety and efficacy of lung volume reduction coil treatment in patients with both heterogeneous and homogeneous emphysema. Further studies are underway to confirm efficacy in long-term randomized trials. Additional studies are needed to improve the understanding of the predictive factors of response in order to better select the responders to lung volume reduction coil treatment.

REFERENCES

1. Shah PL, Herth FJ. Current status of bronchoscopic lung volume reduction with endobronchial valves. Thorax 2014;69:280–6.

2. Gasparini S, Zuccatosta L, Bonifazi M, et al. Bronchoscopic treatment of emphysema: state of the art. Respiration 2012;84:250–63.

3. Fishman A, Martinez F, Naunheim K, et al. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. N Engl J Med 2003;348:2059–73.

4. Criner GJ, Cordova F, Sternberg AL, et al. The NETT: part I. Lessons learned about emphysema. Am J Respir Crit Care Med 2011;184:763–70.

5. Meyers BF, Patterson GA. Chronic obstructive pulmonary disease. 10: Bullectomy, LVR surgery, and transplantation for patients with chronic obstructive pulmonary disease. Thorax 2003;58:634–8.

6. Sciurba FC, Ernst A, Herth FJ, et al. A randomized study of endobronchial valves for advanced emphysema. N Engl J Med 2010;363:1233–44.

7. Herth FJ, Noppen M, Valipour A, et al. Efficacy predictors of lung volume reduction with Zephyr valves in a European cohort. Eur Respir J 2012;39:1334–42.

8. Herth FJ, Eberhardt R, Gompelmann D, et al. Radiological and clinical outcomes of using Chartis to plan endobronchial valve treatment. Eur Respir J 2013;41:302–8.

9. Herth FJ, Eberhard R, Gompelmann D, et al. Bronchoscopic lung volume reduction with a dedicated coil: a clinical pilot study. Ther Adv Respir Dis 2010;4:225–31.

10. Slebos DJ, Klooster K, Ernst A, et al. Bronchoscopic lung volume reduction coil treatment of patients with severe heterogeneous emphysema. Chest 2012;142:574–82.

11. Donohue JF. Minimal clinically important differences in COPD lung function. COPD 2005;2:111–24.

12. Hartman JE, Ten Hacken NH, Klooster K, et al. The minimal important difference for residual volume in patients with severe emphysema. Eur Respir J 2012;40:1137–41.

13. Puhan MA, Chandra D, Mosenifar Z, et al. The minimal important difference of exercise tests in severe COPD. Eur Respir J 2011;37:784–90.

14. Jones PW. St George's respiratory questionnaire: MCID. COPD 2005;2:75–9.

15. Jones PW, Quirk FH, Baveystock CM, et al. A self-complete measure of health status for chronic airflow limitation. The St George's Respiratory Questionnaire. Am Rev Respir Dis 1992;145:1321–7.

16. Miller MR, Crapo R, Hankinson J, et al. General considerations for lung function testing. Eur Respir J 2005;26:153–61.

17. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111–7.

18. van Rikxoort EM, de Hoop B, Viergever MA, et al. Automatic lung segmentation from thoracic computed tomography scans using a hybrid approach with error detection. Med Phys 2009;36:2934–47.

19. Shah PL, Zoumot Z, Singh S, et al. Endobronchial coils for the treatment of severe emphysema with hyperinflation (RESET): a randomized controlled trial. Lancet Respir Med 2013;1:233–40.

20. Shah PL, Slebos DJ, Cardoso PF, et al. Bronchoscopic lung-volume reduction with Exhale airway stents for emphysema (EASE trial): randomized, sham-controlled, multicentre trial. Lancet 2011;378:997–1005.

21. Deslee G, Barbe C, Bourdin A, et al. Cost-effectiveness of lung volume reduction coil treatment in emphysema: STIC REVOLENS. Rev Mal Respir 2012;29:1157–64.

22. Washko GR, Martinez FJ, Hoffman EA, et al. Physiological and computed tomographic predictors of outcome from lung volume reduction surgery. Am J Respir Crit Care Med 2010;181:494–500.

23. Cooper CB. The connection between chronic obstructive pulmonary disease symptoms and hyperinflation and its impact on exercise and function. Am J Med 2006;119:21–31.

24. Garcia-Rio F, Lores V, Mediano O, et al. Daily physical activity in patients with COPD is mainly associated with dynamic hyperinflation. Am J Respir Crit Care Med 2009;180:506–12.

25. Baraldo S, Turato G, Saetta M. Pathophysiology of the small airways in chronic obstructive pulmonary disease. Respiration 2012;84:89–97.

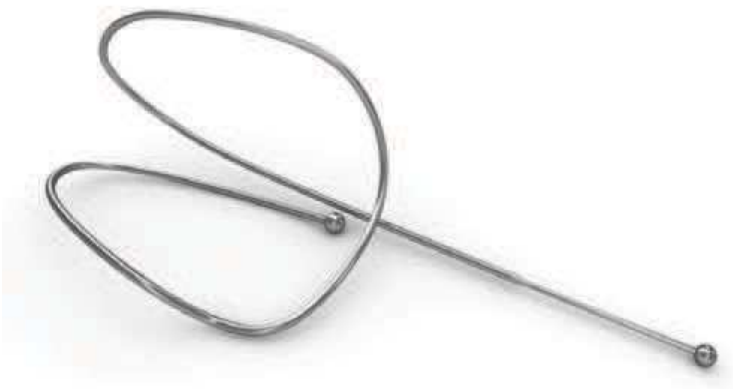
26. Stoller JK, Gildea TR, Ries AL, et al. Lung volume reduction surgery in patients with emphysema and alpha-1 antitrypsin deficiency. Ann Thorac Surg 2007;83(Suppl 1):241–51.

27. Mahler DA, Faryniarz K, Tomlinson D, et al. Impact of dyspnea and physiologic function on general health status in patients with chronic obstructive pulmonary disease. Chest 1992;102:395–401.

28. Naunheim KS, Wood DE, Mohsenifar Z, et al. Long-term follow-up of patients receiving lung-volume-reduction surgery versus medical therapy for severe emphysema by the National Emphysema Treatment Trial Research Group. Ann Thorac Surg 2006;82:431–43.

29. Snell G, Herth FJ, Hopkins P, et al. Bronchoscopic thermal vapour ablation therapy in the management of heterogeneous emphysema. Eur Respir J 2012;39:1326–33.

30. Herth FJ, Gompelmann D, Stanzel F, et al. Treatment of advanced emphysema with emphysematous lung sealant (AeriSeal(R)). Respiration 2011;82:36–45. 986



CHAPTER

9

Long-term follow-up after bronchoscopic lung volume reduction treatment with coils in patients with severe emphysema

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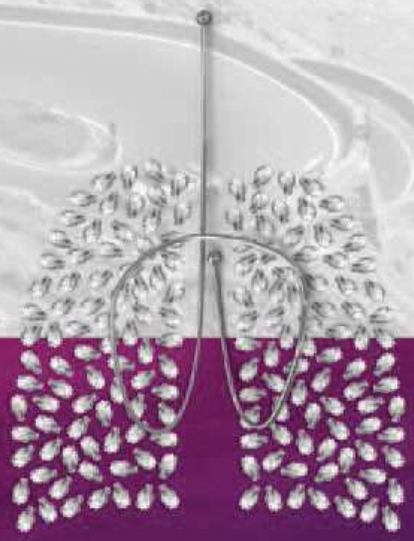


Adapted from

Respirology 2015;20:319-26.

ABSTRACT

Background
Bronchoscopic lung volume reduction coil treatment has been shown to be safe and clinically effective in patients with severe emphysema in the short term; however, long-term safety and effectiveness has not been evaluated.

Objective
The aim of this study was to investigate the long-term safety and effectiveness of lung volume reduction coil treatment in patients with severe emphysema.

Methods
Thirty-eight patients with severe emphysema (median age is 59 years, forced expiratory volume in 1 second is 27% of predicted value) who were treated in lung volume reduction coil clinical trials were invited for a voluntary annual visit. Safety was evaluated by chest X-ray and recording of adverse events and by efficacy by pulmonary function testing, distance on 6 minute walk test and questionnaires.

Results
Thirty-five patients visited the hospital 1 year, 27 patients 2 years and 22 patients 3 years following coil placement. No coil migrations were observed on X-rays.

At 1-year follow-up, all clinical outcomes significantly improved compared with baseline.

At 2 years, residual volume % of the predicted value, modified Medical Research Council (mMRC) and the St. George's Respiratory Questionnaire score (SGRQ) were still significantly improved.

At 3 years, a significant improvement in mMRC score remained, with 40% of the patients reaching the minimal clinically important difference for distance on the 6 minute walk test, and 59% of the patients reaching the minimal clinically important difference for SGRQ.

Conclusion
Follow-up of the patients treated with lung volume reduction coils in our pilot studies showed that the coil treatment is safe with no late pneumothoraces, coil migrations or unexpected adverse events. Clinical benefit gradually declines over time; at 3 years post-treatment, around 50% of the patients maintained improvement in distance on 6 minute walk test, SGRQ and mMRC.

INTRODUCTION

Bronchoscopic lung volume reduction is a new minimally invasive treatment option for patients with severe emphysema.[1] Bronchoscopic lung volume reduction treatment with one-way endobronchial valves, a 'blocking' device, is an efficacious method in a selected group of patients with absence of collateral ventilation.[2,3] For the majority of patients with severe emphysema, a bronchoscopic lung volume reduction treatment that works independently of collateral ventilation, a 'non-blocking' device, must be used. One of the currently investigated non-blocking devices is the lung volume reduction coil (RePneu, PneumRx, Inc., Mountain View, CA, USA). This nitinol coil is bronchoscopically delivered in both lungs in either upper or lower lobe heterogeneous emphysema or homogeneous emphysema,[4,5] thereby compressing diseased parenchyma and radially suspending airways after placement in the lung.

To date, five studies investigating lung volume reduction coil treatment have been published.[4–8] Four non-randomized studies (N=10, N=11, N=16 and N=60 patients)[4,6–8] and one randomized study (N=24 controls and N=23 treated patients)[5] showed that the procedure is feasible, safe and well tolerated. Significant improvements in quality of life, exercise capacity and pulmonary function were observed.[4,5,7,8] Most studies had relatively short follow-up times: 3 months,[5,6] 6 months[4,8] and one study up to 12 months after treatment.[7] To our knowledge, no study investigated a longer follow-up time after lung volume reduction coil treatment. This longer follow-up time is needed to document both safety and effectiveness of the procedure. In our hospital, we performed two pilot studies investigating bronchoscopic lung volume reduction coil therapy, with treatments in 2009 and 2010.

The aim of this study is to investigate the safety and effectiveness of lung volume reduction treatment with coils 1, 2 and 3 years post-treatment in patients with severe emphysema who participated in pilot trials.

SUMMARY AT A GLANCE

This is the first study to investigate the safety and efficacy of the lung volume reduction coil treatment in the long term. At 3 year of follow-up, this treatment showed no long-term unexpected adverse and device-related events, with clinical benefit gradually declining over time.

METHODS

Study population

Between April 2009 and November 2010, 38 patients were treated with the lung volume reduction coil at our institution, in one of two pilot studies (NCT012209084 and NCT013288997). The inclusion and exclusion criteria for both can be found in box 1. Both studies were approved by the University Medical Center Groningen Medical Ethics Committee, and all participants signed informed consents.

Box 1. Study inclusion and exclusion criteria.

Inclusion criteria

- Patient ≥ 35 years of age*
- $FEV_1 \leq 45\%$ of predicted*
- Total lung capacity >100% of predicted*
- Residual volume > 175% of predicted[2]
- Modified medical research council dyspnea score (mMRC) ≥ 2 on mMRC scale of 0-4*
- Non-smoker for more than eight weeks prior to entering the study*
- High resolution CT scan indicates unilateral or bilateral emphysema[1]
- CT scan indicates bilateral heterogeneous emphysema[2]
- Patient read, understood and signed the informed consent form*

Exclusion criteria

- Change in FEV_1 > 20% post-bronchodilator
- Diffusion capacity < 20% predicted
- A history of recurrent clinically significant respiratory infection
- Uncontrolled pulmonary hypertension defined by right ventricular pressure > 50mmHg
- An inability to walk > 140 meters in 6 minutes
- Evidence of other disease that may compromise survival such as lung cancer, renal failure etc.
- Patient is pregnant or lactating
- An inability to tolerate bronchoscopy under moderate sedation or anesthesia
- Clinically significant bronchiectasisGiant bullar > 1/3 lung volume
- Previous LVR surgery, lung transplant or lobectomy
- Patient has been involved in other pulmonary drug studies with 30 days prior to this study
- Patient is taking >20mg prednisone (or similar steroid) daily
- Any use of clopidogrel or coumarines
- Other disease that would interfere with completion of study, follow-up assessments or that would adversely affect outcomes
- Patient has severe homogeneous emphysema by CT scan

*Applicable for both studies
[1]Applicable for study NCT01220908
[2]Applicable for study NCT01328899

Lung volume reduction coil treatment

The lung volume reduction coil procedure has been described before.[4,6] In brief, the coils (RePneu, PneumRx Inc.) are made of shape-memory nitinol wire, range in length from 70 mm to 200 mm to accommodate airways of different sizes and are designed to compress the lung parenchyma. The coils were bronchoscopically placed under general anesthesia in two sequential procedures using fluoroscopy.

Study design
The follow-up period of both studies were 6 months[4] and 12 months[7] after the second treatment. After completing and exiting the study, patients were invited for a voluntary annual follow-up visit. Patients performed pulmonary function measurements, 6 minute walk test and chest X-ray and completed questionnaires. Patients also had a consultation with a physician who reported the patient's health status during the past year.

Measurements
Spirometry, bodyplethysmography and the 6 minute walk test were performed using ERS/ATS guidelines.[9–11] Health-related quality of life was measured by the SGRQ[12] and dyspnea severity by the mMRC scale.[13]

Safety was measured by recording all adverse events reported by the patients during the yearly follow-up visits. The first X-ray after the treatment and the last performed X-ray at final follow-up visit for all participants were assessed for presence of coil migration (defined as displacement of the original post treatment coil position in the segment), atelectasis and consolidation of tissue around the coils.

Pre-treatment decline in forced expiratory volume in 1 second
All available spirometry results of the pre-treatment years were collected from the patient's own hospital, serving as a reference of the expected decline in lung function of our patients.

Lung transplantation
Two patients underwent a lung transplantation: one patient at 1 year and the second patient at 4 years post-treatment. Both patients gave permission for histopathological examination of the explant. The lung tissue was processed according to routine clinical guidelines for confirmation of disease diagnosis and assessment of any potential concurrent disease. Haematoxylin and eosin stains were made on lung sections after careful removal of the nitinol coils, and representative sections were photographed and unedited used for presentation in this study.

Statistical analysis
Due to non-normally distributed data, Wilcoxon signed rank tests were performed to compare the clinical characteristics at 1-, 2- and 3-year follow-up against baseline and to compare if baseline characteristics differed between responders and non-responders at 3-year follow-up. For the responder analyses, we counted the number of patients who reached the earlier established minimal clinically important difference for FEV_1 (100 ml and 10%[14]), residual volume (400 ml[15]), distance on 6 minute walk test (26 meter[16]), and the SGRQ (4 points[17]). The annual change in post-bronchodilator FEV_1 before the treatment was derived from the slope of the regression line for each patient's individual FEV_1 values measured at their own hospital. We only calculated the annual change in FEV_1 of patients when at least three FEV_1 values were available. Paired sample t-tests were performed to compare the difference in the decline in FEV_1 before and after the treatment. P-values < 0.05 were considered statistically significant. IBM-SPSS Statistics (version 20) was used for statistical analysis (IBM, Armonk, NY, USA).

RESULTS

Patients

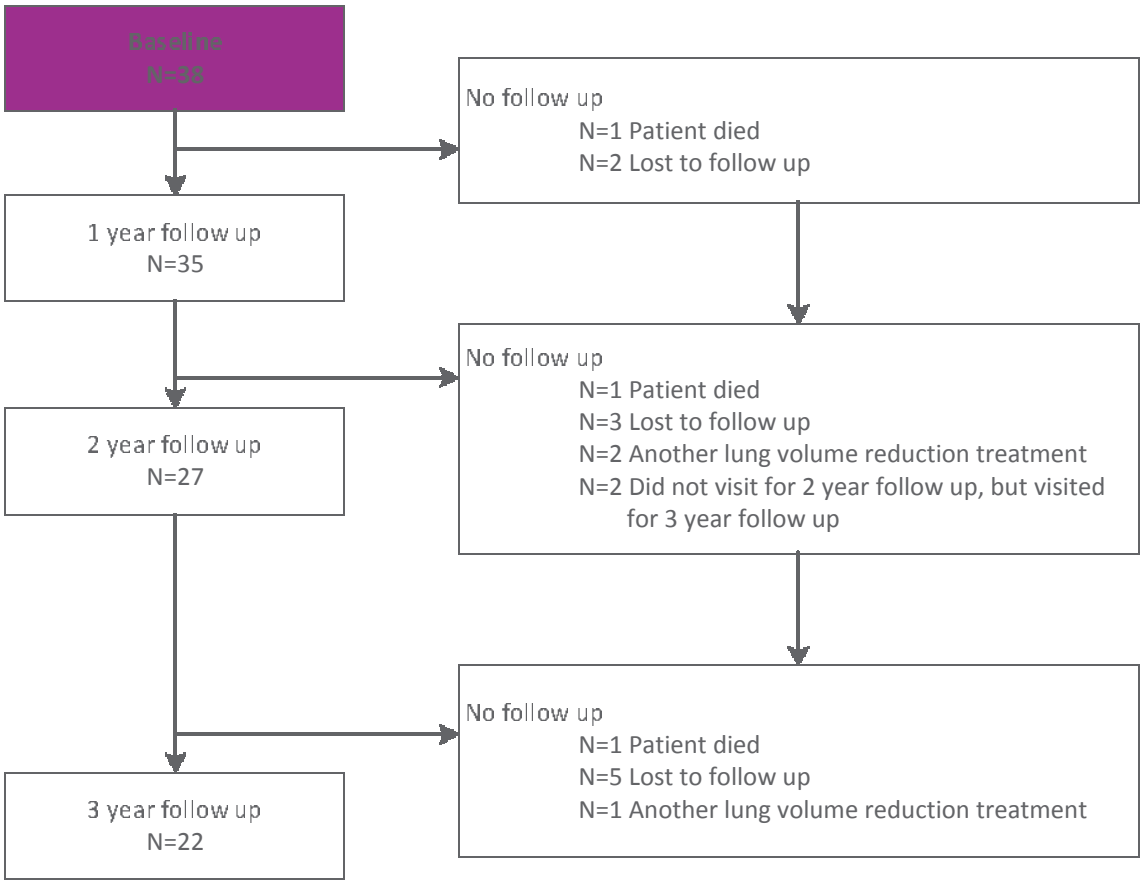
The baseline characteristics of the 38 patients are shown in table 1. One year after the treatment, 35 patients performed follow-up measurements, at 2 years 27 patients and at 3 years 22 patients (figure 1).

Table 1. Baseline characteristics.

Characteristic	Outcome
Female, N (%)	28 (74%)
Age, years	59.2±7.7
BMI, kg/m²	24.9 (18.6-35.4)
Diagnosis emphysema, years	8.9±3.5
Packyears, years	34.7±11.2
Heterogeneous emphysema, N (%)	35 (92%)
FEV_1, % of predicted value	27 (16-42)
GOLD stage III, N (%)	13 (34%)
GOLD stage IV, N (%)	25 (66%)
FVC, % of predicted value	82±15
RV, % of predicted value	228 (155-341)
Ratio of RV to TLC, %	0.61 (0.50-0.74)
mMRC score, N (%)	3.0 (2.0-4.0)
Distance on 6 minute walk test, meter	326±94
SGRQ total score, points	63.2 (36.9-83.0)

Data are presented as number (%), 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: modified Medical Research Council, SGRQ: St. George's respiratory questionnaire.

Figure 1. Flowchart of study participants.



Safety

The adverse events are shown in table 2. Six patients (16%) died during the 3-year follow-up independent of the treatment. The causes of death are reported in table 2. Two patients had a pneumothorax directly after the coil procedure; however, no long-term pneumothoraces occurred. Of the patients, 74% reported a very mild hemoptysis just post-procedure; only one patient reported spontaneous settling of more severe hemoptysis at 3-year follow-up. On the follow-up chest X-rays, we observed no coil migrations, a segmental atelectasis was visible in 3 patients (8%) and consolidation of tissue around some of the coils in 11 patients (29%) (see figure 2 for the first X-ray post-procedure and the follow-up X-ray at 3-year follow-up of two example patients).

Table 2. Number of reported adverse events.

	Baseline to 1 year FU	1 year to 2 year FU	2 year to 3 year FU
	N=35	N=27	N=22
Death*	1 (3%)	3 (8%)	2 (6%)
Pneumothorax	2 (6%)	0 (0%)	0 (0%)
Pneumonia	16 (46%)	2 (7%)	1 (5%)
Hospitalization due to COPD exacerbation	18 (51%)	10 (37%)	8 (36%)
Haemoptysis	0 (0%)	0 (0%)	1 (5%)

Data are presented as number of patients (%). FU: follow-up. *Percentages of patients who died were calculated based on the total number of patients at baseline. Causes of death (N=6, time post-treatment):

1: 20 months (right upper lobe only): pneumonia of the left lung with pseudomonas sepsis.

2: 10 months (right upper lobe only): end-stage COPD, complicated by an osteoporotic Th6 fracture causing immobilization and severe pain.

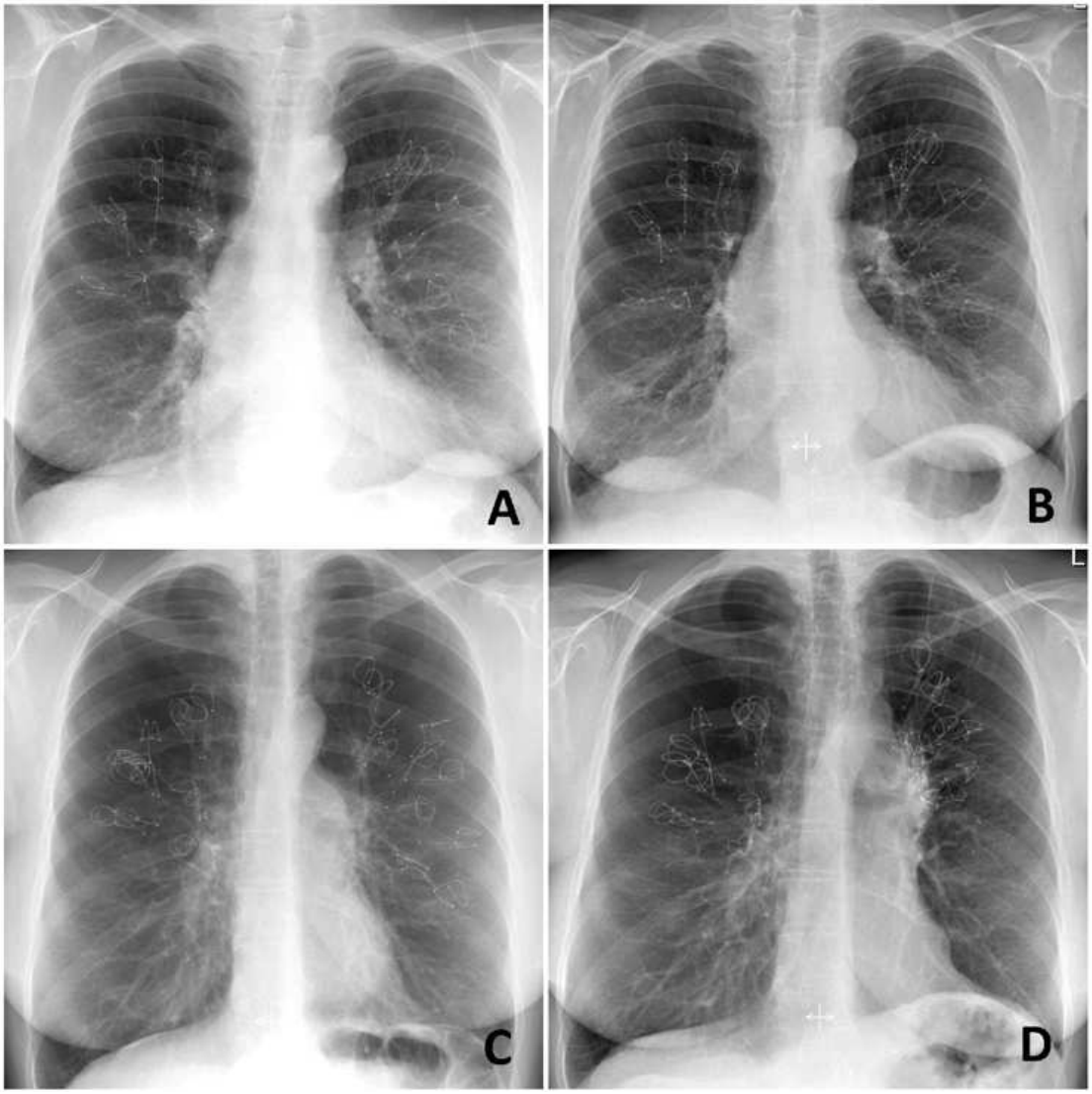
3: 16 months (bilateral upper lobe): end-stage COPD with cor pulmonale.

4: 16 months (bilateral upper lobe): sudden cardiac death not further specified.

5: 38 months (bilateral upper lobe): myocardial infarction.

6: 35 months (bilateral upper lobe): end-stage COPD.

Figure 2. The first X-ray after the procedure and last available follow-up X-ray of two example patients.



(A) Directly after the second procedure in patient 1.
(B) Three years after the procedure in patient 1 without any changes.
(C) Directly after the second procedure in patient 2.
(D) Three years after the procedure in patient 2, showing some 'crowding' of the coils in the left upper lobe resulting in volume reduction and a better left hemidiaphragm position.

Effectiveness

At 1-year follow-up, forced vital capacity, residual volume, ratio of residual volume to total lung capacity, mMRC, distance on 6 minute walk test and SGRQ total score were all significantly improved compared with baseline. At 2-year follow-up, residual volume, mMRC and the SGRQ total score were significantly improved when compared with baseline. At 3-year follow-up, only the mMRC was significantly improved compared with baseline. The other clinical characteristics were not significantly changed at 3 years compared with baseline (table 3).

Table 3. Change in clinical characteristics at 1, 2 and 3 year follow-up.

	1 year FU (N=35)	P value	2 year FU (N=27)	P value	3 year FU (N=22)	P value
FEV_1, Liter	0.2 (-0.2-0.45)	0.171	-0.04 (-0.26-0.36)	0.809	-0.05 (-0.39-0.39)	0.664
FEV_1, % predicted	1 (-6-20)	0.080	-1 (-9-17.)	0.949	0 (-14-19)	0.747
FVC, Liter	0.04 (-0.39-1.13)	0.060	-0.02 (-0.85-1.11)	0.597	0.04 (-0.56-0.91)	0.723
FVC, % predicted	3 (-12-44)	0.014	1 (-25-44)	0.741	6 (-18-38)	0.169
RV, Liter	-0.32 (-1.88-0.68)	<0.001	-0.14 (-1.57-0.92)	0.093	0.07 (-1.67-1.41)	0.629
RV, % predicted	-21 (-91-32)	<0.001	-10 (-83-43)	0.012	-2 (-89-57)	0.509
RV/TLC, %	-3.6 (-21.3-5.7)	<0.001	-0.2 (-18.6-10.3)	0.428	1.5 (-19.0-12.5)	0.664
mMRC, score	0 (-3-2)	0.007	0.0 (-3.0-1.0)	0.007	-0.5 (-3-1)	0.039
6MWD, meter	31 (-110-185)	0.010	-12 (-140-238)	0.696	-32 (-120-177)	0.970
SGRQ,points	-4 (-44-13)	0.005	-8(-40-20)	0.032	-7 (-30-21)	0.101

Data are presented as median (range) in change between follow-up and baseline and P values. Baseline and follow-up measurements were compared with Wilxocon signed-rank test. 6MWD, distance on 6 minute walk test; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; mMRC, modified Medical Research Council; RV, residual volume; SGRQ, St George's Respiratory Questionnaire; TLC, total lung capacity.

The number of patients reaching the MID for FEV_1 ranged from 20–30% (absolute change) to 30–40% (relative change) throughout the 1- to 3-year follow-up. The number of patients reaching the minimal clinically important difference for residual volume decreased during the 1- to 3-year follow-up, from 51% to 19%. The number of patients reaching the minimal clinically important difference for distance on 6 minute walk test decreased during the 1- to 3-year follow-up from 57% to 40%. The number of patients reaching the minimal clinically important difference for SGRQ ranged from 50% to 60% throughout the 1- to 3-year follow-up (table 4). No differences were found in baseline characteristics between patients who reached the minimal clinically important difference for SGRQ or distance on 6 minute walk test at 3-year follow-up

Table 4. Minimal clinically important difference responder analysis.

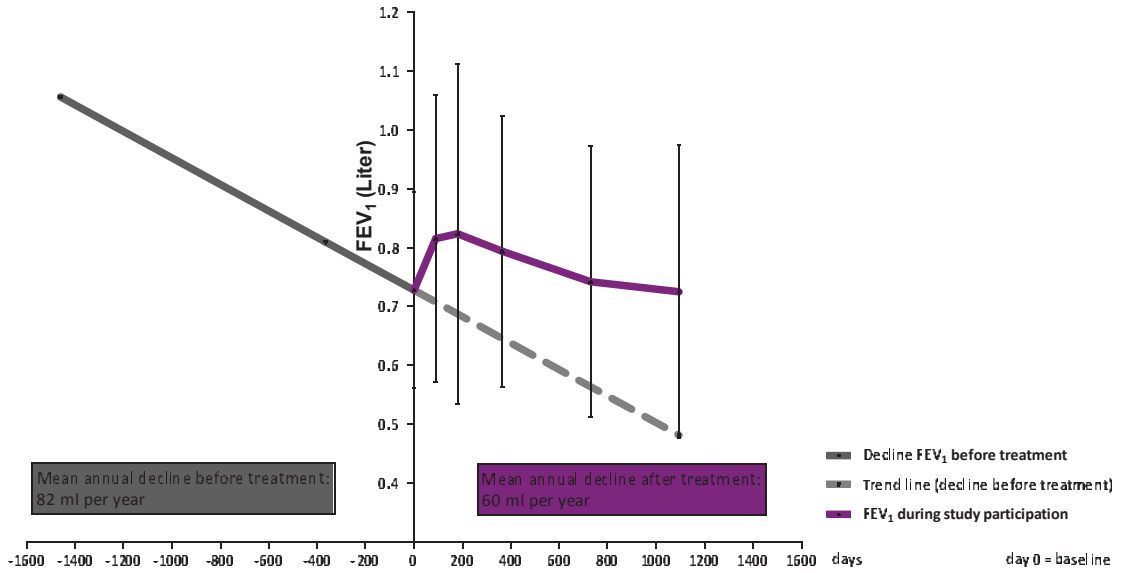
	MCID	6 months (N=35)	1 year (N=35)	2 years (N=27)	3 years (N=22)
Forced expiratory volume in 1-second	**≥ 100 ml**	11 (31%)	8 (23%)	5 (19%)	7 (33%)[2]
Forced expiratory volume in 1-second	**≥ 10%**	17 (49%)	11 (31%)	9 (33%)	8 (38%)[2]
Residual volume	**≤ 400 ml**	18 (51%)	14 (40%)	8 (30%)	4 (19%)[2]
Distance on 6 minute walk test	**≥ 26 meter**	20 (57%)	20 (57%)	7 (27%)[1]	8 (40%)[3]
St. George's respiratory questionnaire	**≤ 4 points**	22 (63%)	18 (51%)	17 (63%)	13 (59%)

Data are presented as N (%). MCID denotes minimal clinically important difference. [1]N=26, [2]N=21, [3]N=20.

Pre-treatment decline in FEV_1

At least three previously performed FEV_1 measurements were available for 30 of the 38 patients (79%). The median number of available measurements was 9 (range 3–23) and the median number of days for the first available measurement before treatment was 1989 days (range: 292–4376). The mean decline in FEV_1 before the lungvolume reduction coil treatment was −0.082 Liter per year (standard deviation: 0.073). This was significantly different compared with the mean decline in FEV_1 during study participation (mean decline: −0.036 Liter per year, P = 0.018). The decline in FEV_1 after more than 6 months of follow-up did not significantly differ compared with the decline before the treatment (mean decline: −0.060 Liter per year, P = 0.45 (figure 3).

Figure 3. Decline in FEV_1 before and after the lung volume reduction coil treatment.



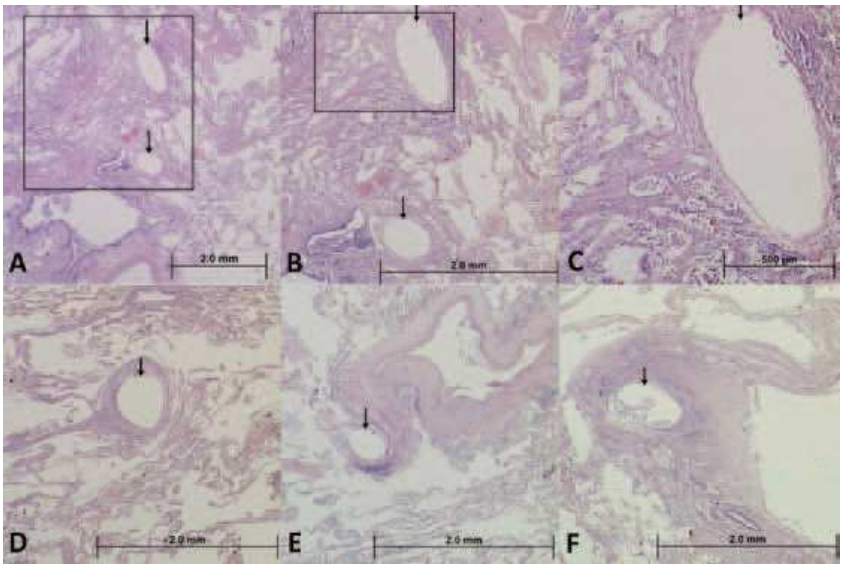
Baseline and post-treatment FEV_1 shown as mean ± standard deviation.

Lung transplant explant evaluation

On gross macroscopic evaluation of the lung explants, the coils could be identified in the main segmental and sub-segmental airways. No vascular disruptions were noticed, nor were there any abscess formations in the coiled regions. Histopathological examination revealed in both patients, besides presence of emphysematous tissue, a thin, compressed capsule of tissue around the imprints of the airways with a slight inflammatory reaction. It was unclear whether these changes represent pre-existing pathology in these patients or if this is associated with device placement.

In the 1-year specimen, the presence of interstitial fibrosis of alveolar septa with the device 'capsule' and the surrounding alveolar parenchyma was visible. In the 4-year specimen, the device imprint in the airways was surrounded by a well-organized fibrous capsule comprised of compressed, concentric rings of stroma, and this was also found in the alveolar parenchyma, where the device imprint was in an area of more dense fibrous tissue. No abundant inflammatory reaction or infection was found in either explant (see figure 4).

Figure 4. Histology of transplanted lungs of two patients.



Photomicrograph, haematoxylin and eosin stain. **(A)** Low power magnification of lung tissue demonstrating two device imprints (arrows) in the alveolar parenchyma. **(B)** Higher magnification of the boxed area in image **(A)** demonstrating the two device imprints in tissue. At this magnification, it is evident that there is a thin, compressed capsule of tissue around the imprints with no other significant inflammatory reaction present. This image also demonstrates the presence of interstitial fibrosis of alveolar septa along the left hand side of the image. **(C)** Higher magnification of the boxed area in image **(B)** demonstrating a closer view of the device capsule and the surrounding alveolar parenchyma. **(D)** Low power magnification of a single device imprint in the alveolar parenchyma (arrow). The imprint is surrounded by a well-organized fibrous capsule comprised of compressed, concentric rings of stroma. Pre-existing emphysema (enlarged alveolar spaces) is also evident in this image. **(E)** Low power magnification of a single device imprint (arrow) in the alveolar parenchyma adjacent to a pulmonary vein. **(F)** Low power magnification of a single device imprint in an area of more dense fibrous tissue. The device capsule contains a mild degree of inflammation. **(A-C)** Patient 1 year after LVR-coil treatment; **(D-F)** patient 4 years after lung volume reduction coil treatment.

DISCUSSION

This was the first study that investigated the long-term safety and effectiveness of bronchoscopic lung volume reduction treatment with nitinol coils. In this trial, we followed our first pilot study patients over the years and showed that the treatment is safe in the long term. After 1 year, the treatment was found to be clinically effective compared with baseline, with a median gradual decline of the clinical benefits over time, with 3-year follow-up approaching similar parameters to the pre-treatment baseline for the overall group and with a responder rate of 59% of the patients reaching minimal clinically important difference for SGRQ and 40% for distance on 6 minute walk test at 3 years.

In the 3-year follow-up of our pilot studies, patients showed that the lung volume reduction coil treatment was safe in the long term. We witnessed no late pneumothoraces, no coil migrations, no major hemoptysis, no major infectious complications or unexpected adverse device events and no treatment-related deaths. The 3-year survival in our group (84%) is in line with survival reports in the literature for comparable patient populations. Lange et al.[18] reported a 74.2% 3-year survival, and a 55–65% 3-year survival is reported when using Collaborative Cohorts to Assess Multicomponent Indices of COPD in Spain, Global Initiative for Chronic Obstructive Lung Disease, or ATS/Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index in Chronic Obstructive Pulmonary Disease severity criteria.[19]

Evaluation of post-lung transplant-explanted lung tissue showed that the proximal and mid portions of the coils can still be found in the segmental and sub-segmental airways, encapsulated by some fibrotic/organizing reaction, with occasionally the most distal part of the coils being encapsulated in the surrounding lung tissue, but with no signs of serious inflammatory or infectious reactions. These findings indicate that there is tendency of the airways and lung tissue to slowly organize around the coils, which might be due to local tissue stress, compression and micro movements of the coils.

The treatment was beneficial for a large group of patients after 1 year, with overall mean clinical parameters returning to baseline values at 3 years. Unfortunately, we did not have a control group in which we could investigate the natural decline of clinical parameters. However, the National Emphysema Treatment Trial (NETT) study[20] that investigated lung volume reduction surgery in severe emphysema patients with a median follow-up of 4.3 years reported that clinical parameters like SGRQ declined in both the treatment and control group.[20] To estimate the natural rate of functional decline in our patients, we collected all available pre-treatment spirometries. We found that the rate of decline did not change after the lung volume reduction coil treatment but that treatment increased FEV_1 to the extent that return to pre-treatment baseline levels occurred only after approximately 3 years (figure 3). That the rate of decline did not change is unsurprising; two other studies investigating lung volume reduction surgery also showed that the rate of decline after surgery was comparable with the rate of decline before surgery.[21,22]

We believe it is as important to evaluate clinical significance as it is with statistical significance of outcomes from treatment. Therefore, we also investigated whether patients reached the minimal clinically important difference for FEV_1, residual volume, distance on 6 minute walk test and SGRQ at each time point. However, a confounding factor is that most minimal clinically important differences were calculated for short-term changes, ranging from 115 to 616 months post-intervention. A long-term minimal clinically important difference (for example 3 years) could be lower than a minimal clinically important difference for the short term. Therefore, the minimal clinically important differences used in our analyses could underestimate the number of meaningful responders at 3 years. Unfortunately, this is not known and would be interesting to investigate. We did not find any predictive factors to identify responders at 3-year follow-up. However, our sample size was too small to be able to evaluate this in detail. Current ongoing large randomized controlled trials (NCT01608490 and NCT01822795) will possibly give more insight in the best responder profile for this treatment.

Long-term follow-up after bronchoscopic lung volume reduction treatment with coils has not been investigated before. A few other studies investigating other lung volume reduction techniques included at least 12 months follow-up. The NETT study[20] found that 20% of the patients improved more than 8 points on the SGRQ total score 3 years after lung volume reduction surgery (patients who died or were lost to follow-up were considered not improved). When we apply the same rules for improvement, 31% of our patients (N=11) improved more than 8 points after 3 year. As in our study, the NETT study also found a larger improvement in the quality of life in the long term than in exercise capacity. Another study investigated the effect of lung sealant therapy for emphysema in 16 patients two years after the initial treatment.[23] They found a much higher number of patients who reached the minimal clinically important difference for FEV_1 two years after the treatment, which is 50% compared with 19% in our population. Not much literature to date has been published on longer-term follow-up data for bronchoscopic lung volume reduction devices. Three small cohort studies investigated long-term follow-up of endobronchial valve treatment. Venuta et al.[24] showed promising results after 3 and 5 years follow-up. Unfortunately, patient loss to follow-up was not taken into account, and paired statistical analyses were not used, making the result difficult to interpret. A retrospective study by Kotecha et al.[25] showed that 6 out of 16 patients (38%) had sustained long-term improvements in FEV_1 (change > 0), which is comparable with our study (31% at 2-year follow-up: 11 out of 27 patients). Furthermore, Hopkinson et al.[26] showed that the occurrence of atelectasis following endobronchial valve treatment was associated with prolonged survival at 6 years follow-up.

The major disadvantage of our study is the non-controlled design and possible selection bias of patients who volunteered for yearly follow-up visits after participating in one of our pilot studies. Although a large number of patients did visit our hospital yearly, the results at 2 year and 3 year follow-up should be interpreted with caution as patients with worse response could be presumed less likely to return for follow-up. It would be useful to investigate the long-term efficacy and safety of the lung volume reduction coil treatment in a randomized controlled intervention study with long-term follow-up.

Currently, a large (N=315) randomized controlled trial with 5-year follow-up is enrolling patients and will give additional insight into the long-term effectiveness and safety of coil treatment (Lung Volume Reduction Coil Treatment in Patients With Emphysema Study: NCT01608490).

CONCLUSION

Follow-up of our very first pilot patients showed that lung volume reduction coil treatment is safe in the long term, with no late pneumothoraces, coil migrations or unexpected adverse events. Clinical benefit gradually declines over time; at 3 years post-treatment, around 50% of the patients maintained improvement in distance on 6 minute walk test, SGRQ and mMRC.

Acknowledgments

We would like to acknowledge Dr T. Spangler (VDx Veterinary Diagnostics, Davis, USA) for the histopathologically evaluation of the explanted lung tissue. Furthermore, we would like to thank the pulmonary function technicians of the University Medical Center Groningen for their dedicated pulmonary function testing.

REFERENCES

1. Mineshita M, Slebos DJ. Bronchoscopic interventions for chronic obstructive pulmonary disease. Respirology 2014; 19: 1126–37.

2. Herth FJ, Eberhardt R, Gompelmann D, et al. Radiological and clinical outcomes of using Chartis to plan endobronchial valve treatment. Eur. Respir. J. 2013; 41: 302–8.

3. Shah PL, Herth FJ. Current status of bronchoscopic lung volume reduction with endobronchial valves. Thorax 2014; 69: 280–6.

4. Slebos DJ, Klooster K, Ernst A, et al. Bronchoscopic lung volume reduction coil treatment of patients with severe heterogeneous emphysema. Chest 2012; 142: 574–82.

5. Shah P, Zoumot Z, Singh S, Bicknell SR, et al., RESET Trial Study Group. Endobronchial coils for the treatment of severe emphysema with hyperinflation (RESET): a randomized controlled trial. Lancet Respir.Med. 2013; 1: 233–40.

6. Herth FJ, Eberhard R, Gompelmann D, Slebos DJ, Ernst A. Bronchoscopic lung volume reduction with a dedicated coil: a clinical pilot study. Ther. Adv. Respir. Dis. 2010; 4: 225–31.

7. Deslee G, Klooster K, Hetzel M, et al. Lung volume reduction coil treatment for patients with severe emphysema, a European multicenter feasibility trial. Thorax 2014; 69: 980–6.

8. Klooster K, ten Hacken N, Franz I, et al. Lung volume reduction coil treatment in COPD patients with homogeneous emphysema: a prospective feasibility trial. Respiration 2014; 88: 116–25.

9. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur. Respir. J. 2005; 26: 319–38.

10. Wanger J, Clausen JL, Coates A, et al. Standardisation of the measurement of lung volumes. Eur.Respir. J. 2005; 26: 511–22.

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

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

13. 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: 581–6.

14. Donohue JF. Minimal clinically important differences in COPD lung function. COPD 2005; 2: 111–24.

15. Hartman JE, Ten Hacken NH, Klooster K, et al. The minimal important difference for residual volume in patients with severe emphysema. Eur. Respir. J. 2012;40: 1137–41.

16. Puhan MA, Chandra D,Mosenifar Z, et al., NETT Research Group. The minimal important difference of exercise tests in severe COPD. Eur. Respir. J. 2011; 37: 784–90.

17. Jones PW. St: George's Respiratory Questionnaire. MCID. COPD 2005; 2: 75–9.

18. Lange P, Marott JL, Vestbo J, et al. Prediction of the clinical course of chronic obstructive pulmonary disease, using the new GOLD classification: a study of the general population. Am. J. Respir. Crit. Care Med. 2012; 186: 975–81.

19. Almagro P, Martinez-Camblor P, Soriano JB, et al. Finding the best thresholds of FEV1 and dyspnea to predict 5-year survival in COPD patients: the COCOMICS study. PLoS ONE 2014; 9: e89866.

20. Naunheim KS, Wood DE, Mohsenifar Z, et al. Long-term follow-up of patients receiving lung-volume reduction surgery versus medical therapy for severe emphysema by the National Emphysema Treatment Trial Research Group. Ann. Thorac. Surg. 2006; 82: 431–43.

21. Gelb AF, McKenna RJ Jr, Brenner M, et al. Lung function 5 yr after lung volume reduction surgery for emphysema. Am. J. Respir. Crit. Care Med. 2001; 163: 1562–6.

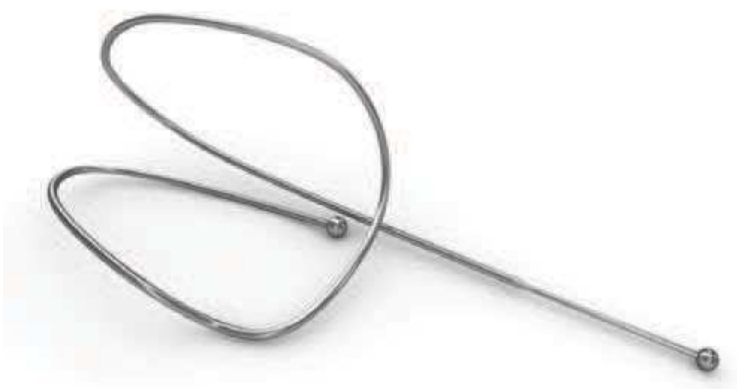
22. Travaline JM, Gaughan JP, Furukawa S, Criner GJ. Effect of bilateral lung volume reduction surgery on FEV_1 decline in severe emphysema. COPD 2005; 2: 203–8.

23. Kramer MR, Refaely Y, Maimon N, et al. Two-year follow-up in patients treated with emphysematous lung sealant for advanced emphysema. Chest 2013; 144: 1677–80.

24. Venuta F, Anile M, Diso D, et al. Long-term follow-up after bronchoscopic lung volume reduction in patients with emphysema. Eur. Respir. J. 2012; 39: 1084–9.

25. Kotecha S, Westall GP, Holsworth L, et al.. Long-term outcomes from bronchoscopic lung volume reduction using a bronchial prosthesis. Respirology 2011; 16: 167–73.

26. Hopkinson NS, Kemp SV, Toma TP, et al. Atelectasis and survival after bronchoscopic lung volume reduction for COPD. Eur.Respir. J. 2011; 37: 1346–51.



CHAPTER

10

Lung volume reduction coil treatment in COPD patients with homogeneous emphysema: A prospective feasibility trial

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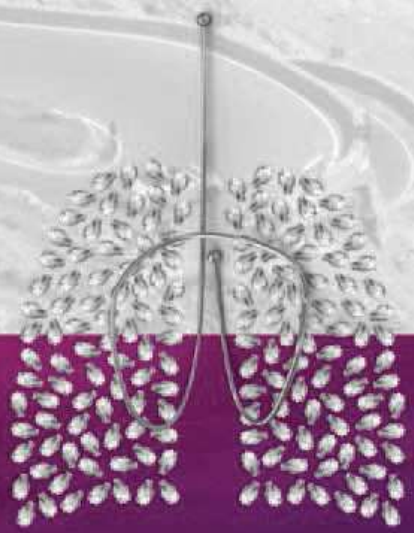


Adapted from

Respiration 2014;88:116-25.

ABSTRACT

Background
In patients with heterogeneous emphysema, surgical and bronchoscopic lung volume reduction treatments are available. However, for patients with homogeneous emphysema these treatments are hardly investigated and seem less effective. Bronchoscopic lung volume reduction coil treatment has been shown to be effective in patients with heterogeneous emphysema, but this treatment has not been exclusively investigated in homogeneous emphysema.

Objectives
The aim of this study was to investigate the safety and efficacy of lung volume reduction coil treatment in patients with homogeneous emphysema.

Methods
In this single-arm, open-label study, patients received a maximum of 12 coils (PneumRx Inc., Mountain View, California, USA) in each upper lobe in two sequential procedures. Tests were performed at baseline and at 6 months. The primary endpoint was the improvement from baseline in distance on 6 minute walk test after treatment.

Results
Ten patients with severe airway obstruction and hyperinflation were treated. A median of 11 (range 10–12) coils were placed in each lung. Two COPD exacerbations and one small pneumothorax were recorded as serious adverse events.

At 6 months, distance on 6 minute walk test had improved from 289 to 350 meter (P=0.005); forced vital capacity from 2.17 to 2.55 Liter (P=0.047); residual volume from 5.04 to 4.44 Liter (P=0.007) and St. George's Respiratory Questionnaire from 63 to 48 points (P=0.028).

Conclusion
Lung volume reduction coil treatment in homogeneous patients improves hyperinflation, airway resistance, exercise capacity and quality of life with an acceptable safety profile. The benefit of lung volume reduction coil treatment is not limited to patients with heterogeneous emphysema, and patients with homogeneous emphysema can benefit as well.

INTRODUCTION

COPD is a major cause of chronic morbidity and mortality worldwide and it will become the third leading cause of death by 2020.[1] COPD is characterized by a spectrum of small airway abnormalities (the 'bronchitic' component) and lung parenchymal destruction (the 'emphysema' component). Parenchymal destruction of the lung reduces the protective elastic recoil forces on the airways leading to increased airway collapsibility. This emphysema component may contribute importantly to the airflow limitation due to the narrowed and obLiterated small airways in COPD.[2] These combined pathophysiological effects may result over time in clinically important air trapping and hyperinflation. Lung hyperinflation correlates with important patient-related outcomes, such as dyspnea, exercise performance, physical activity and quality of life.[2]

In patients with severe COPD, the currently available pharmacological treatment options have only limited effectiveness. For patients with the emphysematous COPD phenotype, surgical and bronchoscopic therapeutic interventions exert an effect through reducing hyperinflation.[3] However, until now only patients with severe emphysema and a heterogeneous distribution have been selected for surgical or bronchoscopic interventions. The National Emphysema Treatment Trial showed that lung volume reduction surgery improved quality of life, pulmonary function and exercise tolerance, especially in patients with predominant upper lobe emphysema.[4]

Over the past years a number of new minimally invasive bronchoscopic lung volume reduction modalities have been investigated, these being mainly effective in patients with heterogeneous emphysema. Endobronchial one-way valve placement has shown to be of benefit especially in a small subgroup of patients with heterogeneous emphysema.[5,6] Using a lung sealant for emphysema, upper lobe target sites have a greater treatment response in heterogeneous emphysema when compared to homogeneous disease.[7]

We recently showed that lung volume reduction coil treatment in patients with upper lobe heterogeneous emphysema improved quality of life, hyperinflation and exercise capacity.[8] One major randomized sham-controlled trial investigating the use of bronchoscopic airway bypass, dedicated to patients with homogeneous emphysema, showed short-term but no sustainable benefit.[9]

To date, there is no solid evidence for the efficacy of bronchoscopic lung volume reduction treatment in patients with exclusively homogeneous emphysema defined by strict computed tomography criteria. Therefore, we investigated the safety and efficacy of lung volume reduction coil treatment in patients with homogeneous emphysema.

METHODS

Patients and Study Design

This study was a prospective, open-label, single-center cohort trial for patients with severe emphysema and a homogeneous distribution assessed on computed tomography (CT) scan. All patients were on optimal medication and completed a rehabilitation program. The main inclusion and exclusion criteria are shown in box 1. The protocol included a 6 month follow-up after the first treatment. This study was approved by the University Medical Center of Groningen medical ethics committee (NL36612.042.11). The trial is registered with ClinicalTrials.gov (No. NCT01421082). All study patients gave written informed consent.

Box 1. The main inclusion and exclusion criteria.

Inclusion criteria

- > 35 years of age
- CT scan indicating homogeneous emphysema
- Post- bronchodilator FEV_1 ≤ 35% of predicted value
- Post- bronchodilator FVC ≤ 90% of predicted value
- Total Lung Capacity > 120% of predicted value
- Residual Volume > 225% of predicted value
- RV/TLC > 60%
- Dyspnea score >1 on mMRC scale of 0-4
- Stopped smoking for a minimum of 6 months prior to procedure
- Signed informed consent

Exclusion criteria

- Carbon monoxide diffusion capacity < 20% of predicted value
- History of recurrent clinically significant respiratory infection
- Uncontrolled pulmonary hypertension defined by right ventricular pressure >50mmHg
- Inability to walk >140 meter in 6 minutes
- Evidence of other disease that may compromise survival such as lung cancer
- Clinically significant bronchiectasis
- Giant bullae >1/3 lung volume
- Previous lung volume reduction surgery, lung transplant or lobectomy
- >20 mg prednisone daily
- Antiplatelet agent which can not be weaned off prior to procedure

Lung volume reduction coil and the lung volume reduction coil procedure

The lung volume reduction coil is an implantable, shape-memory nitinol device. The system (RePneu ®, Lung Volume Reduction Coil System, PneumRx Inc., Mountain View, California, USA) consists of a single-patient use delivery system with a cartridge, catheter, guidewire, forceps and coils (figure 1). These self-actuating coils are delivered via the bronchoscope into the airway in a straight configuration and recover to a non-straight pre-determined shape upon deployment. The coil is available in 3 lengths (100 mm, 125 mm and 150 mm) to accommodate different airway lengths. The distal and proximal ends of the coil are designed to reside in sub segmental airways.

Figure 1. Components of the lung volume reduction coil system.

In this study, the bronchoscopy was performed under general anesthesia using a 9.0 mm endotracheal flexible tube and flexible bronchoscope (BF180; Olympus, Hamburg, Germany; 2.8 mm working channel, 6.0 mm outer diameter), and coil deployment was completed under fluoroscopic guidance. Following recovery from anesthesia, patients stayed in the hospital overnight for observation. The lung volume reduction coil procedure in this study was performed as described previously,[8] with placement of a maximum of twelve coils per upper lobe and by using a standardized segmental treatment algorithm independent of specific CT findings. During the first procedure the coils were placed into the right upper lobe (RB2-RB1-RB3) and 2 months later during the second procedure the coils were placed into the left upper lobe (LB1/2-LB3-LB4, leaving segment LB5 untreated because of its proximity to the heart). Patients received as per our standard interventional bronchoscopy prophylactic regimen a 5-day course of prednisolone (25 mg once daily), starting 2 days before the procedure, and a 5-day course of azithromycin (250 mg once daily), starting on the procedure day.

Follow-Up

Safety was assessed by recording all the adverse events that occurred. Adverse events were divided into those occurring in the first 30 days after each coil treatment, the period which we regarded to be related to the actual procedure (labeled as the recovery period), and those occurring in the 31 days between procedure 1 and procedure 2, and the 31 days from procedure 2 to the 6 month follow-up after procedure 1 (labeled as the follow-up period).

At baseline and the final 6 month follow-up we performed a high-resolution volume CT scan, measured quality of life using the St. George's Respiratory Questionnaire (SGRQ),[10] assessed the health status of COPD patients using the Clinical COPD Questionnaire (CCQ)[11] and measured the disability of our patients with the modified Medical Research Council dyspnea scale (mMRC).[12] We performed pulmonary function testing (spirometry, body plethysmography and diffusion capacity using a Jaeger MasterScreen™ Body Plethysmograph) and impulse oscillometry according to the ATS/ERS guidelines[13,14] and using reference values from workers of the European Community for Steel and Coal.[15] The 6 minute walk test was done according to ATS recommendations,[16] and was prospectively chosen as the primary endpoint. Besides the conventional body plethysmography pressure/volume loops, we also obtained resistance/volume graphs using an automated conversion program (CareFusion Corporation).[17] The resistance/volume graph gives information about the combination of the within breath course of the dependency of absolute lung volume on airway resistance.

CT Scan Qualifications and Analysis

The chest CT scan slice thickness was 1.0 mm, made at 120 kV/210 mAs. All quantifications were performed with CIRRUS Lung 13.10 (Diagnostic Image Analysis Group, Nijmegen, The Netherlands; Fraunhofer MEVIS, Bremen, Germany).[18,19,20] The lungs and lobes were automatically segmented and visually inspected. Emphysema severity was computed as an emphysema score, i.e. the percentage of voxels below –950 Hounsfield units, and this score was computed for the entire lung and per lung lobe. The airways were excluded to ensure that only lung parenchyma was analyzed. Patients were considered to be homogeneous and eligible when the difference in destruction between ipsilateral lobes was less than 15% using this analysis for both lungs.

Statistics

Safety is reported descriptively. The other results are presented as medians and range. The Wilcoxon signed-rank test was used to assess the statistical significance of changes from baseline. A P value of <0.05 was considered statistically significant. IBM SPSS Statistics version 20 was used for all analyses.

RESULTS

Patients

We screened 11 patients between November 2011 and July 2012. One patient was not eligible due to a residual volume less than 225% of the predicted value. Ten patients were treated bilaterally in two sequential procedures (see table 1 for demographics and baseline characteristics).

The median emphysema CT destruction scores of the treated patients expressed as the percentage relative area of destruction below –950 Hounsfield units for the right lung were: upper lung 39% (range 34–51) and lower lung 33% (range 26–53), and for the left lung were: upper lung 37% (range 29–47) and lower lung 35% (range 24–49).

Table 1. Demographics and baseline characteristics (N=10).

Characteristic	
Age, years	54 (44-66)
Female/Male	9/1
Packyears, number	40 (25-60)
BMI, kg/m^2	22.4 (16.2-28.7)
FEV_1, % of predicted value	22 (19-31)
FVC, % of predicted value	69 (52-89)
Ratio of FEV_1 to FVC, %	29 (19-38)
TLC, % of predicted value	141 (121-182)
RV, % of predicted value	253 (217-375)
Ratio RV to TLC, %	68 (61-74)
Raw, % of predicted value	272 (180-403)
DL_{CO}, % of predicted value	31 (23-42)
$PaCO_2$, kPa	5.9 (4.4-6.9)
PaO_2, kPa	9.2 (7.3-10.6)
Patients on home oxygen, N (%)	6 (60%)
Distance on 6 minute walk test, meter	289 (160-485)
mMRC, points	2.5 (2-4)
SGRQ total score, points	63 (45-79)
CCQ, points	3.0 (1.9-3.8)

Data are presented as median (range) where appropriate.

Lung volume reduction coil procedure

In 10 patients we performed 20 procedures in which a total of 227 coils were placed, with a median of 11 (range 10–12) coils positioned in 33 (range 22–55) minutes per lung. No periprocedural technical events occurred, and all coils were placed as planned. Of the 227 coils placed in this study, none had to be replaced or removed (see table 2 for all procedural results). The median hospital stay after the procedure was 1 (range 1–4) night.

Table 2. Lung volume reduction coil procedural results.

Variable	
Number of procedures	20
Procedure time, minutes	33 (22-55)
Post-procedure hospital stay, days	1 (1-4)
Coils per procedure, number	11 (10-12)
Total coils implanted	227
Upper, Right Lobe	113
Upper, Left Lobe	114
Length of coils used	
100 mm	123
125 mm	104
150 mm	0

Data are presented as median (range) where appropriate.

Safety

No adverse events occurred due to anesthesia in these patients with severe COPD. After the procedure, we observed only one small 2-cm apical pneumothorax which spontaneously resolved without a chest tube. No other serious adverse events occurred in the first 30 days following each procedure (defined as the recovery period). During the follow-up period (31 days after procedure 1 to procedure 2, and 31 days after procedure 2 to 6 months after procedure 1) two serious adverse events were reported due to COPD exacerbations requiring hospitalization. All the adverse events in this study were managed with standard care and no life-threatening events occurred. All adverse events are listed in table 3.

Table 3. Serious adverse events and adverse events.

	Recovery period (cumulative after each procedure to 30 days)	Follow-up period (up to 6 months after first procedure)
Serious Adverse Events		
Pneumothorax	1	0
COPD exacerbation requiring hospitalization	0	2
Pneumonia	0	0
Respiratory Failure	0	0
Death	0	0
Adverse Events		
Slight haemoptysis (<5 ml)	5	0
Chest discomfort (non-cardiac)	6	0
COPD exacerbation	3	5
Dyspnea	0	1
Bronchitis	1	0
Hypertension	0	1
Hypermenorrhoea	0	1

Investigator reported serious adverse events and adverse events in numbers. The recovery period is defined ≤30 days after each lung volume reduction coil procedure. The follow-up period is defined as 31 days post-procedure 1 to pre-procedure 2 and 31 days post-procedure 2 to 6 month follow-up post procedure 1.

Efficacy

Comparing the 6 month follow-up results to baseline revealed that bilateral lung volume reduction coil treatment had resulted in a significant improvement in exercise performance as measured by an increase in distance on 6 minute walk test from 289 to 350 meter (P=0.005). Quality of life also showed significant improvements as measured by a change in SGRQ total score from 63 to 48 points (P=0.028) and by a change in CCQ score from 3.0 to 2.3 points (P=0.007). There was also a significant improvement in lung volumes, with forced vital capacity improving from 2.17 to 2.55 Liter (P=0.047) and residual volume from 5.04 to 4.44 Liter (P=0.007). Airway resistance changed significantly with a decrease in airway resistance from 0.82 to 0.62 kPa*second/Liter (P= 0.009). CT scan analysis showed a significant decrease in lung volume in the treated upper lobes from 3204 to 2941 ml (P=0.037), while in non-treated lower lobes there was no change in lung volumes (3496–3489 ml, P=0.646). All baseline and 6 month follow-up results are shown in table 4.

Table 4. Baseline and 6-month follow-up results (N=10).

	Baseline	6 months FU	P value
Distance on 6 minute walk tets, meter	289 (160-485)	350 (192-520)	0.005
FEV_1, Liter	0.58 (0.45-0.93)	0.69 (0.56-1.02)	0.102
FVC, Liter	2.17 (1.82-3.17)	2.55 (1.81-3.67)	0.047
ITGV, Liter	6.02 (5.28-7.19)	5.84 (4.63-7.13)	0.009
TLC, Liter	7.48 (6.46-9.08)	7.36 (5.97-9.09)	0.037
RV, Liter	5.04 (4.14-6.57)	4.44 (3.57-5.68)	0.007
RV, % of predicted value	253 (217-375)	231 (172-325)	0.007
Ratio RV to TLC, %	68 (61-74)	60 (55-67)	0.005
Airway resistance, kPa*second/Liter	0.82 (0.54-1.21)	0.62 (0.43-0.91)	0.009
SGRQ Total, points	63 (45-79)	48 (25-68)	0.028
SGRQ Symptoms, points	63 (13-79)	36 (2-69)	0.017
SGRQ Activity, points	89 (72-100)	79 (35-93)	0.018
SGRQ Impacts, points	44 (16-71)	32 (14-64)	0.074
CCQ, points	3.0 (1.9-3.8)	2.3 (1.4-3.0)	0.007
mMRC, points	2.5 (2-4)	2.0 (1-4)	0.16
CT volume right upper lobe, ml	1514 (1096-1700)	1399 (1126-1702)	0.053
CT volume left upper lobe, ml	1685 (1157-1901)	1547 (1218-1868)	0.037
CT volume treated lobes, ml	3204 (2253-3601)	2941 (2344-3570)	0.037
CT volume untreated lobes, ml	3496 (2172-4262)	3489 (2071-4244)	0.646

Data are presented as median (range).

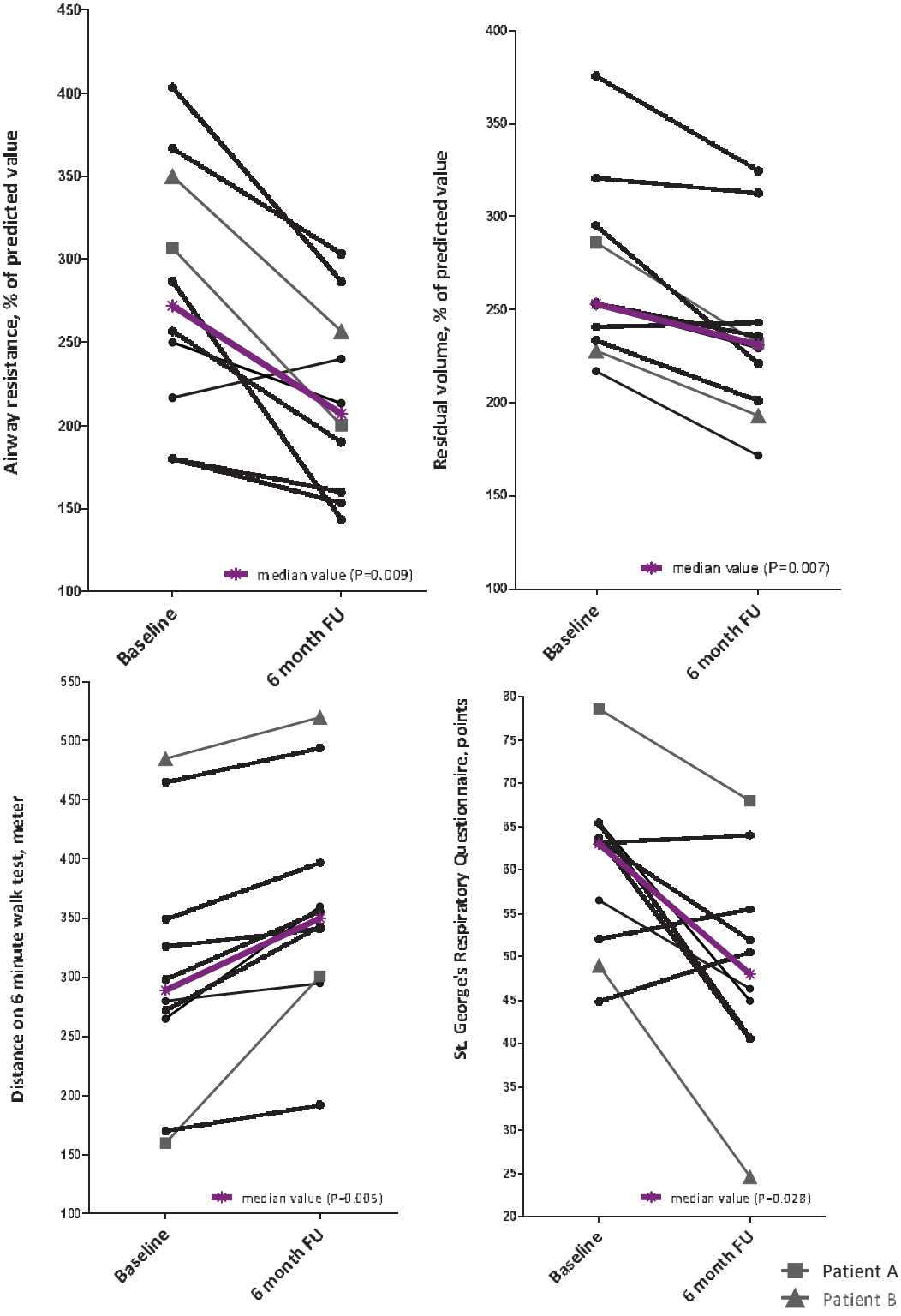
Seventy percent of the patients responded by more than the minimal clinically important difference for the distance on 6 minute walk test,[29,30,31], residual volume[21], SGRQ[22] and CCQ[11] (table 5). Individual patient data at baseline and follow-up for the distance on 6 minute walk test, SGRQ, residual volume and airway resistance are shown in figure 2.

Table 5. Responder rates at 6 months after lung volume reduction coil treatment.

	MCID	6 months FU
Residual volume	≥ 0.43 Liter[21]	70% (N=7 of 10)
Distance on 6 minute walk test	≥ 26 meter[29,30]	70% (N=7 of 10)
Distance on 6 minute walk test	≥ 48 meter[31]	50% (N=5 of 10)
St. George's respiratory questionnaire	≥ 4 points[22]	70% (N=7 of 10)
St. George's respiratory questionnaire	≥ 8 points	70% (N=7 of 10)
Clinical COPD questionnaire	≥ 0.4 points[11]	80% (N=8 of 10)

Data are presented as the percentage of patients responding. MCID denotes minimal clinically important difference.

Figure 2. Individual patient data at baseline and at 6 month follow-up for distance on 6 minute walk test, SGRQ, residual volume and airway resistance.



DISCUSSION

In this trial we demonstrated for the first time prospectively the feasibility and safety of lung volume reduction coil treatment specifically in patients with severe COPD and homogeneous emphysema. Despite the small sample size of this study, lung volume reduction coil treatment significantly improved hyperinflation, exercise tolerance and quality of life, with 70% of the patients responding by at least the minimal clinical important difference.

In this severely diseased group of patients it was safe to perform the lung volume reduction coil procedure under general anesthesia. To minimize the anesthesiology time and reduce the risk of bilateral procedure-induced complications, we performed the lung volume reduction coil treatment in two consecutive procedures 8 weeks apart. No anesthesia-related events occurred. The adverse events profile seen with the lung volume reduction coil treatment appears acceptable as only one small apical pneumothorax not needing chest tube drainage occurred directly after the procedure, whereas two COPD exacerbations were recorded as serious adverse event during the follow-up. Beforehand, one would expect extra coughing and sputum production after implanting more than 20 coils in diseased airways. However, the symptoms score assessed with the SGRQ demonstrated a significant reduction.

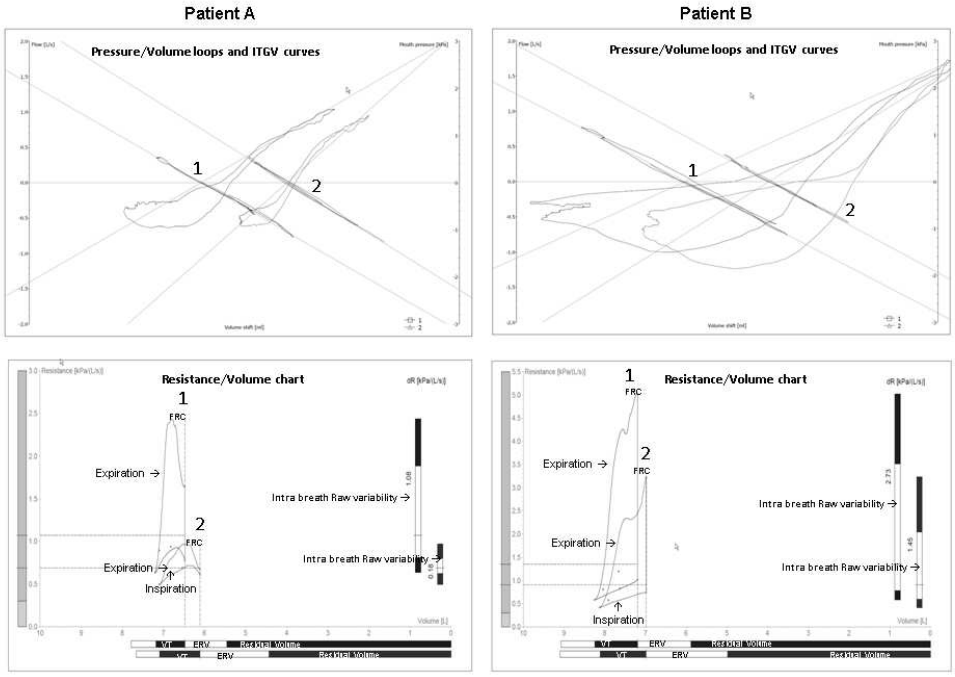
In patients with severe emphysema, only patients with a heterogeneous disease distribution have so far been seen as the proper candidates for effective treatment by both lung volume reduction surgery[4] and a number of bronchoscopic lung volume reduction modalities, such as endobronchial one-way valve placement,[5] thermal vapor ablation[23] and using lung sealant.[24] In patients with homogeneous emphysema all these procedures showed limited efficacy.

The first clinical pilot lung volume reduction coil study, using a maximum of 6 coils per lobe, suggested that patients with homogeneous emphysema might not benefit as well as patients with heterogeneous emphysema.[25] In the second lung volume reduction coil study only patients with heterogeneous emphysema were included and treated with a new generation coil, with the number of coils implanted in the lobe increased.[8] In our study we now show a high responder efficacy rate in patients with homogeneous emphysema. These results are also supported by recently published randomized controlled trial data (RESET trial) where both heterogeneous as well as homogeneous emphysema patients had improved quality of life, exercise tolerance and hyperinflation at 3 months after lung volume reduction coil treatment compared to controls.[26] Future prospective randomized controlled trial data will have to confirm our findings. Currently, two larger (N=315 and N=100) randomized controlled trials using coils in both heterogeneous and homogeneous populations are underway (NCT01608490 and NCT01822795).

In our study, we observed a significant decrease in airway resistance as measured by body plethysmography and by forced oscillation after bilateral lung volume reduction coil treatment. Beforehand, one might expect that implantation of coils inside the airways would obstruct airflow and increase airway resistance. Apparently, the mechanical properties of the lung are improved by the treatment and, importantly, our study also suggests that the lung

parenchyma in subjects with homogeneous emphysema is healthy enough to transfer the elastic recoil forces to the airways. The effects of our coil treatment on airway patency were substantial since we found significant improvements in airway resistance, despite the fact that improved residual volumes lead to reduced airway patency and, thus, underestimation of improved airway resistance. To illustrate this we took the example of 2 patients before and after treatment (figure 3) and plotted 'resistance/volume' graphs. The interpretation of body plethysmography measurement is traditionally based on the results of the lung volumes and the airway resistance. The graphic presentation of the airway resistance is normally displayed as pressure/volume loops. Important intra-breath information incorporating inhomogeneity of ventilation, expiratory flow limitation or airways closure is not presented in this form. When combining the 'traditional' airways resistance (Raw) loop and the intra-thoracic gas volume (ITGV) graphs, the resistance/volume graph can be determined. The maneuver of the body plethysmographic measurement is not changed and there are no additional efforts or maneuvers necessary for the patient. The resistance/volume graph just gives additional information about the volume-dependent airway resistance during a breathing cycle, and can be very useful for any differences before and after treatment. Nevertheless, the mechanisms of action of the coil are not fully understood and additional studies are needed to learn more about the lung compliance, elastic recoil and diaphragm function before and after lung volume reduction coil treatment.

Figure 3. Pressure/volume loops and resistance/volume graphs of 2 patients as an illustrative example of changing lung mechanical properties at baseline and 6 months after lung volume reduction coil treatment.



The resistance/volume graph presents the single breath course of airway resistance, dependent on absolute lung volume. 1=baseline, 2= 6 month follow up. VT = tidal volume (Liter); FRC = functional reserve volume (Liter); ERV = expiratory reserve volume (Liter).

Total lung capacity was both measured by body plethysmography as well as inspiratory HRCT scans. Total lung capacity measured by body plethysmography appeared to be higher compared to total lung capacity measured by HRCT scan. However, the decrease in total lung capacity at the 6 month follow-up using HRCT analysis appears to be greater than the total lung capacity measured by body plethysmography. It is difficult to explain these subtle differences. It is known in COPD patients that total lung capacity can be up to 2 Liters greater than the total lung capacity measured by HRCT scan, especially in patients with severe COPD.[27] Also, the measurement of total lung capacity by body plethysmography is not without errors, particularly in severe COPD, and the same applies to total lung capacity measurement by HRCT.

A limitation of our cohort study is that the design cannot correct for potential placebo effects, which is especially important for the questionnaire data (SGRQ, mMRC and CCQ). However, in other published uncontrolled lung volume reduction device trials using a bilateral intra-bronchial valve placement in patients with severe emphysema, no significant changes were observed in distance on 6 minute walk test or pulmonary function parameters despite this bronchoscopic treatment.[28] Also, the EASE trial data showed no placebo effect for distance on 6 minute walk test, pulmonary function parameters and quality of life questionnaires in a randomized sham-controlled intervention trial design using the airway bypass approach.[9] Although a contribution from a placebo effect cannot be excluded, in our opinion the magnitude of the current effect size exceeds any potential placebo effect.

CONCLUSION

Lung volume reduction coil treatment in patients with homogeneous emphysema is a promising bronchoscopic technique. The procedure is safe and feasible. There is a high responder rate and patients have demonstrated clinically meaningful improvements in exercise capacity, pulmonary function and quality of life at 6 months of follow-up.

Acknowledgments

The authors would like to thank Ruth Hiltermann from the pulmonary department for performing the 6 minute walk tests and obtaining questionnaires, Alie Smidt from the Endoscopy Center for her skillful support during all bronchoscopies performed, the pulmonary function technicians Marga Star, Yvonne Valkema, Margrietha Swierenga, Jan Bouwman and Maria Heuving for their dedicated testing, Martijn Farenhorst for his technical support and Wim Tukker from the department of radiology for his technical management.

REFERENCES

1. Vestbo J, Hurd SS, Agusti AG, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2013; 187: 347–365.

2. Baraldo S, Turato G, Saetta M. Pathophysiology of the small airways in chronic obstructive pulmonary disease. Respiration 2012; 84: 89–97.

3. Fessler HE, Scharf SM, Ingenito EP, et al. Physiologic basis for improved pulmonary function after lung volume reduction. Proc Am Thorac Soc 2008; 5: 416–420.

4. 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. NEngl J Med 2003; 348: 2059–2073.

5. 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.

6. Herth FJ, Eberhardt R, Gompelmann D, et al. Radiological and clinical outcomes of using Chartis to plan endobronchial valve treatment. Eur Respir J 2013; 41: 302–308.

7. Valipour A, Kramer MR, Stanzel F, et al. Physiological modeling of responses to upper versus lower lobe lung volume reduction in homogeneous emphysema. Front Physiol 2012; 3: 387.

8. Slebos DJ, Klooster K, Ernst A, et al. Bronchoscopic lung volume reduction coil treatment of patients with severe heterogeneous emphysema. Chest 2012; 142: 574–582.

9. Shah PL, Slebos DJ, Cardoso PF, et al, EASE trial study group. Bronchoscopic lung-volume reduction with Exhale airway stents for emphysema (EASE trial): randomized, shamcontrolled, multicentre trial. Lancet 2011; 378: 997–1005.

10. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation: the St. George's Respiratory Questionnaire. Am Rev Respir Dis 1992; 145: 1321–1327.

11. Kocks JW, Tuinenga MG, Uil SM, et al. Health status measurement in COPD: the minimal clinically important difference of the clinical COPD questionnaire. Respir Res 2006; 7: 62.

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

13. Miller MR, Crapo R, Hankinson J, Bet al., ATS/ERS Task Force. General considerations for lung function testing. Eur Respir J 2005; 26: 153–161.

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

15. Stocks J, Quanjer PH: Reference values for residual volume, functional residual capacity and total lung capacity. ATS workshop on lung volume measurements – official statement of the European Respiratory Society. Eur Respir J 1995; 8: 492–506.

16. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002; 166: 111–117.

17. Ulmer WT, Schafer T. New insights into physiology and pathophysiology by resistance-volume recordings. J Physiol Pharmacol 2004; 55(suppl 3):149–153.

18. van Ginneken B, Baggerman W, van Rikxoort EM. Robust segmentation and anatomical labeling of the airway tree from thoracic CT scans. Med Image Comput Comput Assist Interv 2008; 11: 219–226.

19. van Rikxoort EM, de Hoop B, Viergever MA, et al. Automatic lung segmentation from thoracic computed tomography scans using a hybrid approach with error detection. Med Phys 2009; 36: 2934–2947.

20. van Rikxoort EM, Prokop M, de Hoop B, et al. Automatic segmentation of pulmonary lobes robust against incomplete fissures. IEEE Trans Med Imaging 2010; 29: 1286–1296.

21. Hartman JE, Ten Hacken NH, Klooster K, et al. The minimal important difference for residual volume in patients with severe emphysema. Eur Respir J 2012; 40: 1137–1141.

22. Jones PW: St. George's Respiratory Questionnaire: MCID. COPD 2005; 2: 75–79.

23. Snell G, Herth FJ, Hopkins P, et al. Bronchoscopic thermal vapour ablation therapy in the management of heterogeneous emphysema. Eur Respir J 2012; 39: 1326–1333.

24. Herth FJ, Eberhardt R, Ingenito EP, Gompelmann D. Assessment of a novel lung sealant for performing endoscopic volume reduction therapy in patients with advanced emphysema. Expert Rev Med Devices 2011; 8: 307–312.

25. Herth FJ, Eberhard R, Gompelmann D, Slebos DJ, Ernst A. Bronchoscopic lung volume reduction with a dedicated coil: a clinical pilot study. Ther Adv Respir Dis 2010; 4: 225–231.

26. Shah PL, Zoumout Z, Singh S, et al. Endobronchial coils for the treatment of severe emphysema with hyperinflation (RESET): a randomized controlled trial. Lancet Respiratory 2013; 1: 233.

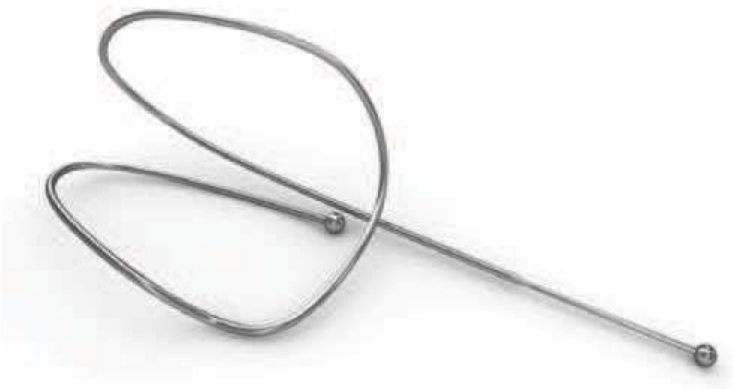
27. Garfield JL, Marchetti N, Gaughan JP, Steiner RM, Criner GJ. Total lung capacity by plethysmography and high-resolution computed tomography in COPD. Int J Chron Obstruct Pulmon Dis 2012; 7: 119–126.

28. Sterman DH, Mehta AC, Wood DE, et al. IBV Valve US Pilot Trial Research Team. A multicenter pilot study of a bronchial valve for the treatment of severe emphysema. Respiration 2010; 79: 222–233.

29. Puhan MA, Chandra D, Mosenifar Z, et al. National Emphysema Treatment Trial (NETT) Research Group. The minimal important difference of exercise tests in severe COPD. Eur Respir J 2011; 37: 784–790.

30. Holland AE, Hill CJ, Rasekaba T, et al. Updating the minimal important difference for six-minute walk distance in patients with chronic obstructive pulmonary disease. Arch Phys Med Rehabil 2010; 91: 221–225.

31. Wise RA, Brown CD. Minimal clinically important differences in the six-minute walk test and the incremental shuttle walking test. COPD 2005; 2: 125–129.



CHAPTER

11

The lung volume reduction coil for the treatment of emphysema: a new therapy in development

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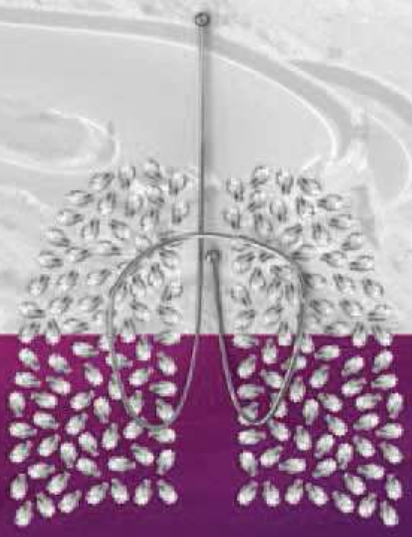


Adapted from

Expert Review of Medical Devices 2014;11:481-9.

ABSTRACT

Lung volume reduction coil treatment is a novel therapy for patients with severe emphysema. In this bilateral bronchoscopic treatment, approximately 10 coils per lobe are delivered under fluoroscopic guidance in two sequential procedures.

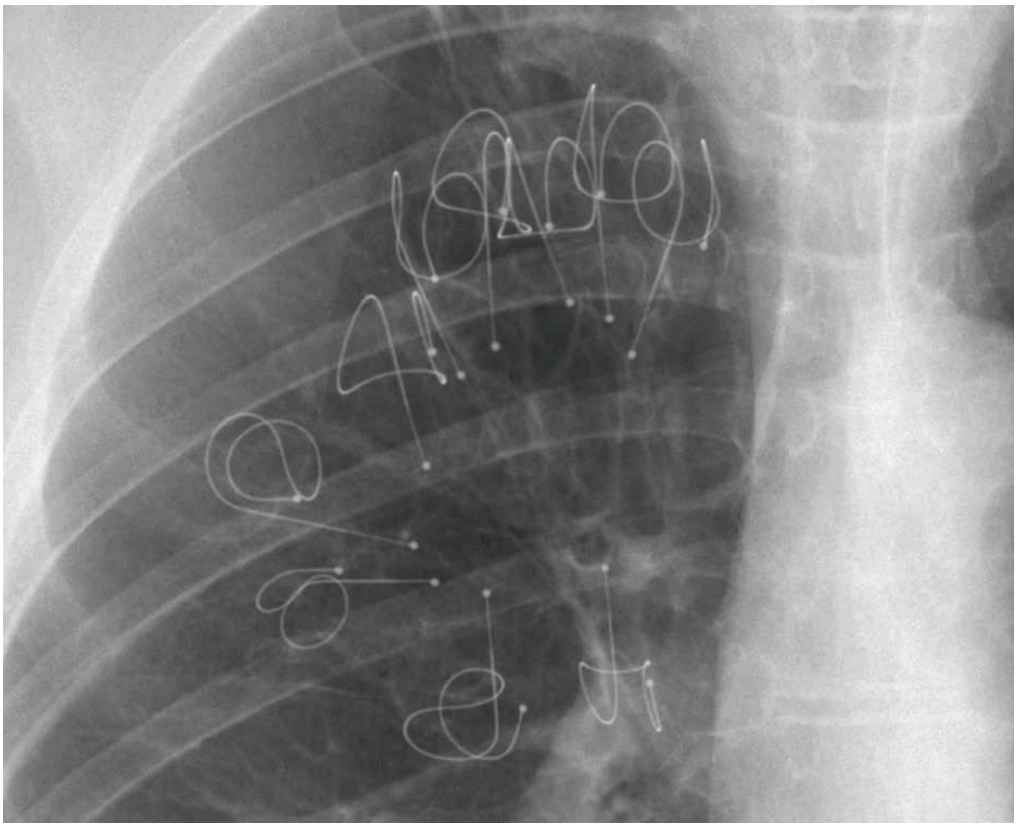
The lung volume reduction coil reduces lung volume by compressing the most destructed areas of the lung parenchyma and restores the lung elastic recoil. Both patients with upper- and lower-lobe predominant emphysema as well as a homogeneous emphysema distribution can be treated.

Lung volume reduction coil treatment results in an improvement of pulmonary function, exercise tolerance and quality of life. The lung volume reduction coil treatment has been evaluated in several European clinical trials since 2008 and received CE mark approval in 2010. Currently, two large multicenter randomized controlled trials are underway in Europe and North America to assess the efficacy and safety of the lung volume reduction coil treatment at 12 months compared with usual care.

In this review, we share our experience with the lung volume reduction coil treatment.

The lung volume reduction coil treatment is a new bronchoscopic therapy for the treatment of patients with severe chronic obstructive pulmonary disease (COPD) (figure 1). Within the COPD phenotypes, the lung volume reduction coil treatment has shown to be effective and has been most extensively tested in the emphysematous, and severely hyperinflated phenotypes. Effective and durable effects have been shown for both upper- and lower-lobe heterogeneous emphysema as well as homogeneous emphysema. Furthermore, the coil works independently of collateral flow.

Figure 1. Part of a X-ray showing 10 coils placed into the right upper lobe.



COPD is one of the major disease entities in the world, affecting millions of people worldwide and an important cause of death.[1] COPD is almost always caused by exogenous factors, like cigarette smoke, air pollution and indoor cooking.[2] Additionally, genetic and endogenous factors contribute to a wide variety in disease susceptibility. COPD constitutes two major disease phenotypes: chronic bronchitis and emphysema. However, these two may show important overlap and include both bronchopathic changes as well as small airways involvement.[3] In patients with COPD, cigarette smoke-induced chronic inflammation results in airway and lung parenchyma damage. This associates with reduced tissue elasticity and decreased elastic recoil leading to increased airway collapse during exhalation. These physiological effects lead to so-called air trapping and progressive increase in lung volume, called hyperinflation.

Hyperinflation reduces the efficiency of the inspiratory muscles, particularly the diaphragm, and leads in emphysema patients to dyspnea, limited exercise capacity and reduced quality of life. When these hyperinflated patients perform exercise, the phenomena of 'dynamic hyperinflation' may occur. Apart from the above-described static hyperinflation, even mild exercise may lead to progressive air trapping and reduced inspiratory capacity, in the end leading to severe feelings of dyspnea.[4]

To date, there is not one single therapy available that will cure COPD. Patients with advanced stages of COPD suffer on a daily basis, and despite a lot of different supportive treatments available, there is a big need for additional treatments for COPD patients. Indeed, modest reductions in symptoms and exacerbation frequency can be achieved by pharmacological interventions. Also smoking cessation and supplemental oxygen therapy may change the prognosis in COPD, whereas pulmonary rehabilitation improves dyspnea, exercise capacity and quality of life.[5] In selected patients, two effective surgical procedures are available for the treatment of severe emphysema: lung volume reduction surgery, and lung transplantation (for all COPD phenotypes). However, both interventions are very invasive and carry a high morbidity and mortality risk.[6] Also the shortage of qualified surgeons to actually perform lung volume reduction surgery and lack of donor lungs available for lung transplantation make these therapies rare. Because of the need for additional therapeutic options, in the last decade, several novel bronchoscopic techniques have been developed or are currently under investigation. These innovative bronchoscopic approaches are minor invasive when compared with lung volume reduction surgery, and are associated with a less overall morbidity and mortality.

Previously investigated bronchoscopic techniques that showed promise, but are not available anymore

The airway bypass procedure

Airway bypass is a bronchoscopic technique designed to release trapped air in patients with severe homogeneous emphysema and abundant collateral flow, by creating extra-anatomic fenestrations. To keep this newly created extra-anatomic tract patent, the bypass is supported with paclitaxel-coated stents.[7] Findings of a large multicenter randomized full-sham controlled trial showed that the airway bypass could be safely created and at day one the airway bypass released trapped air and significantly improved pulmonary function. However, the effect was not sustained at 6 months due to problems with stent patency.[8] Future efforts will have to show if airway bypass patency can be achieved, and revive this proof-of-concept therapy.

Biological lung volume reduction

The AeriSeal® Emphysematous Lung Sealant System was developed to achieve lung volume reduction in patients with upper-lobe predominant heterogeneous emphysema or homogeneous emphysema.[9,10] This bronchoscopic treatment delivers foam of synthetic polymer and a cross-link compound that seals and collapses lung tissue at the sub segmental level in the most diseased areas of the lung. In addition, local inflammation is induced,

followed by fibrosis and sub segmental atelectasis, resulting in the desired volume reduction. This mechanism of action makes this treatment suitable for the treatment of patients independent of collateral ventilation. The device has received CE Mark approval in Europe.[11] In 2012, a large multicenter randomized controlled trial started to demonstrate the safety and efficacy of the AeriSeal treatment in patients with advanced upper-lobe predominant emphysema.[12] Although the efficacy response to the treatment looked promising, the safety issues involved were challenging, especially managing the post-treatment inflammatory response to the sealant. This has led to uncertainty regarding the potential for future product approval, and operations have been aborted in December 2013. Maybe in the future, sequential bilateral or targeted lesion approach still remains valid indication for this therapy.

Current bronchoscopic treatments under investigation

In the past years, based on the publication of an increasing number of clinical trials, presentations on major symposia and individual exiting case stories, a lot of awareness has been created for these new bronchoscopic lung volume reduction treatments. However, to date no published evidence-based, or 'taskforce' guidelines on bronchoscopic lung volume reduction are available. However, based on the current evidence in the literature[10,11,13,14] and supported by expert opinions[15,16] the absence of collateral ventilation between individual segments in the emphysematous lung is important to assess.

Treatments that aim at complete lobar occlusion in the absence of collateral ventilation, or as surrogate, have a complete interlobar fissure on chest computed tomography, are the key predictors for clinical success in response to the total occlusion of a lobe by using one-way valve treatment. Using the active measurement of collateral flow by the Chartis system® (Pulmonx Corporation, Redwood City, CA, USA) will identify up to 75% of responders to one-way valve treatment. Previous clinical trials using a 'blocking technique' also showed that the number of patients with absence of collateral flow between the adjacent lobes in an unselected heterogeneous emphysema patient group was around 25%. This implies that the majority of emphysema patients has collateral flow between adjacent lobes, and consequently cannot be treated with a blocking device. The majority of patients with severe emphysema thus will have to rely on development of techniques that work independently of collateral flow, or so-called 'non-blocking' devices.

Another important factor that drives response to bronchoscopic lung volume reduction is the level of heterogeneity in emphysema distribution between upper and lower lobes. As well as for blocking- and non-blocking techniques, greater emphysema heterogeneity resulted in a better response to treatment.[7,9,10,13,15] On the other hand, not many bronchoscopic lung volume reduction treatments have been prospectively evaluated in exclusively homogeneous emphysema patients yet, where only for the lung volume reduction coil treatment limited, but successful, prospective data are available.

Presently, there are four bronchoscopic lung volume reduction treatment devices that are still under clinical investigation to proof efficacy. All treatments already received CE Mark approval in Europe and are commercially available in certain countries. In the USA, these devices are only for investigational use limited by federal law (table 1).

Table 1. Bronchoscopic lung volume reduction treatment devices which are still under clinical investigation.

Device	Emphysema type	Current investigation by U.S. federal law
Blocking devices		
Endobronchial valve		
Zephyr® Endobronchial valve Pulmonx Corp. USA CE Mark since 2008	heterogeneous no collateral flow upper and lower lobes	NCT01796392 (LIBERATE study); Estimated primary completion date: DEC/2015 (N=183)
Intrabronchial valve		
IBV™ Valve Spiration Inc. USA CE Mark since 2008	heterogeneous no collateral flow upper and lower lobes	NCT01812447 (EMPROVE study); Estimated primary completion date: SEP/2015 (N=270)
Non-blocking devices		
Thermal vapour ablation		
InterVapor™ System Uptake Medical, USA CE Mark since 2011	heterogeneous upper lobe	NCT01719263 (STEP-UP study); Estimated primary completion date: MAR/2015 (N=69)
Lung volume reduction coil		
RePneu® LVRC System PneumRx Inc. USA CE Mark since 2010	heterogeneus homogeneous upper and lower lobes	NCT01608490 (RENEW study); Estimated primary completion date: SEP/2014 (N =315)

Current investigation by U.S. federal law (Source ClinicalTrials.gov January 2014)

Blocking devices

Endobronchial valves

Endobronchial one-way valve (EBV; Zephyr®, Pulmonx Corporation, Redwood City, CA, USA) treatment reduces the lung volume in patients with heterogeneous emphysema, who do not have significant collateral ventilation.

Post-hoc analysis of a large randomized controlled trial demonstrated that a subgroup of emphysema patients have statistically and clinically significant improvements in quality of life, pulmonary function and exercise tolerance[15] when a technical perfect treatment was performed, and the patients had a heterogeneous disease with complete fissures. In a next trial, the Chartis system, which can actually measure collateral ventilation, showed that responders can be identified up 75%.[16] Since 2011, a European prospective single-center randomized controlled trial (STELVIO trial, NTR2876) is underway to investigate the efficacy of the treatment in patients with high heterogeneity with proven absence of collateral ventilation compared with standard optimal medical care alone.

Endobronchial valve treatment is not approved by the U.S. federal law (FDA) and is considered investigational. Endobronchial valve treatment is commercially available outside the USA on a large scale, with an estimated 5000 patients treated worldwide. In 2013, a large multicenter randomized controlled trial (LIBERATE trial) started to investigate the safety and effectiveness of the endobronchial valve treatment. This trial is FDA supported and will be used for future product approval, with an estimated study completion in December 2015. Endobronchial valve treatment can be effective in a selected group of COPD patients with advanced heterogeneous emphysema.

Intrabronchial valves

The intrabronchial valve (IBV; IBV™ Valve Spiration Inc., Redmond, WA, USA) treatment is a technique for severe COPD patients with upper-lobe predominant emphysema. The intrabronchial valve is an investigational device designed to redirect air from the less healthy to the more healthy parts of the lung to reduce hyperinflation. In contrast to the treatment with the Zephyr's endobronchial valves, both lungs are treated, and one segment of a target lobe will not be occluded to prevent lobar atelectasis.[17] Recently, a large randomized controlled trial has demonstrated that the modality of bilateral treatment without complete lobar occlusion is not effective in patients with heterogeneous emphysema.[18] However, unilaterally placed intrabronchial valves with complete occlusion of one entire lobe in patients with complete fissures can improve lung function, exercise capacity and quality of life, when compared with the above-described 'classical' intrabronchial valve approach.[19] Currently, intrabronchial valve treatment is commercially available outside the USA and despite lack of supporting clinical trial data, it is almost only used for total lobar occlusion. Not surprisingly, in 2013, the manufacturing company switched its entire treatment approach and started a large multicenter randomized controlled trial to investigate the safety and effectiveness of the intrabronchial valve treatment aiming at lobar atelectasis in patients with complete interlobar fissure. This trial is also supported by the FDA and will be used in future product approval, with the estimated study completion in September 2015.

Non-blocking devices

Thermal vapor ablation

Thermal vapor ablation (InterVapor™ System Uptake Medical®, Tustin, CA, USA) has been studied in COPD patients with upper-lobe predominant emphysema.[14,20,21] Thermal vapor ablation is an investigational device and uses heated water vapor to produce a thermal reaction to the lung tissue. The heated vapor results in a localized inflammatory reaction followed by permanent fibrosis. An open-label single-arm safety and efficacy study showed that the procedure is well tolerated and the expected inflammatory response can be managed with standard medical care. Improvements were seen in lung function, quality of life and exercise capacity.[14] However, follow-up trials showed, similar to the AeriSeal System, safety issues with high energy dosages and bilateral treatments. Just recently, the company reset its strategy by choosing lower energy levels and performing a sequential bilateral treatment. To test this approach, a multicenter randomized controlled trial has been started last year to investigate the safety and effectiveness of this new thermal vapor ablation treatment approach. This trial is also supported by the FDA. The estimated study completion is June 2015.

Introduction of new treatment: the RePneu lung volume reduction coil system

The RePneu lung volume reduction coil system (RePneu lung volume reduction coil system, PneumRx Inc., Mountain View, CA, USA) is a device designed to compress the areas of the most destructed lung parenchyma to reduce lung volume, and restore elastic recoil of these areas. In December 2012, a large multicenter randomized controlled trial was started to compare outcomes after 12 months follow up between the treatment group (lung volume reduction coil system plus optimal medical therapy) and control group (optimal medical therapy alone) in patients with advanced heterogeneous as well as homogeneous emphysema.[22]

The RePneu lung volume reduction coil system & procedure

The RePneu lung volume reduction coil system is a two-part system. The system consists of a delivery system and of nitinol coils that are available in different sizes. All system components are sterile, single use and disposable. The system is designed to be performed using a therapeutic bronchoscope with a 2.8 mm working channel under fluoroscopic guidance. The lung volume reduction coil procedure aims to treat two lungs. A chest computed tomography will be used to identify target lobes in both lungs. Per procedure only one lobe will be treated. The coils will be placed using a standardized (sub-) segmental treatment algorithm independent of specific computed tomography findings, this to aim at an equal anatomical '3D' distribution of the coils. About 10 coils (8–12) are placed in the upper lobes and up to 14 (10–14) can be placed in the lower lobes. The lung volume reduction coil procedure is preferably performed under general anesthesia.

The RePneu lung volume reduction coil system

Delivery system

The delivery system contains a guidewire, a delivery catheter, a biopsy forceps and a loading cartridge.

• *Guidewire*

The specialized metal flexible guidewire, with an a traumatic tip serves as a guide for the delivery catheter, and is used to identify suitable airways for treatment. The guidewire also facilitates the determination of the appropriate coil length.

• *Delivery catheter*

The catheter, used for the delivery of the coil, is passed over the guidewire and will be aligned with the distal tip of the guidewire under fluoroscopy. The braided construction of the catheter provides column strength, reduces risk of kinking and supports the coil implant during delivery. The tip is soft and radiopaque for visibility under fluoroscopy within the airway.

• *Biopsy forceps*

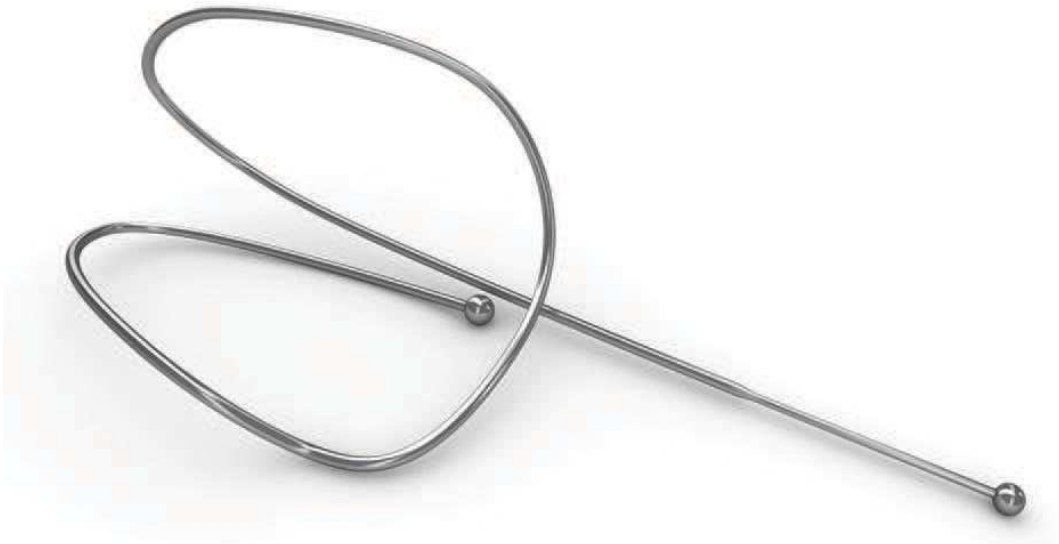
The forceps is used to grasp and fixate the proximal end of the coil, which is then pulled into the loading cartridge. Once loaded, the forceps delivers the coil through the delivery catheter into the targeted airway, and can also be used to reposition or retrieve the coil, if necessary. The forceps has a one-hand locking mechanism to lock the jaws. A marker band indicates when the coil is exiting the catheter.

• *Loading cartridge*

The loading cartridge is slid over the forceps and then the coil will be straightened during the manual uploading into the cartridge. After loading, the cartridge is coupled with the catheter. The luer-lock secures the cartridge to the catheter.

The coil

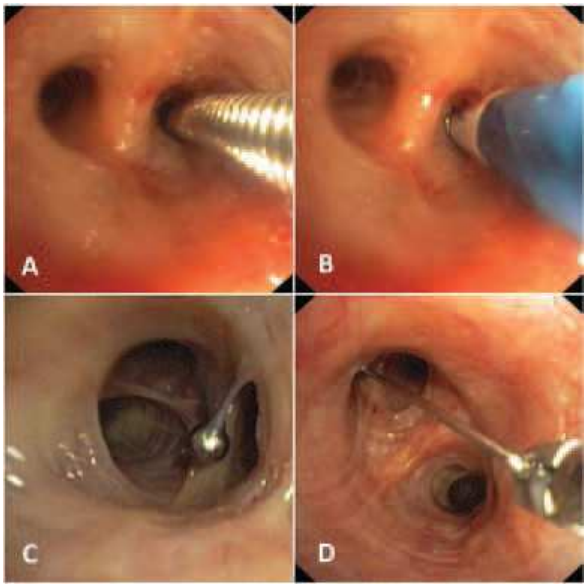
The coil is composed of nitinol (a nickel–titanium alloy), a biocompatible super-elastic material that has been used extensively in implantable medical devices.[21,23,24] Nitinol is also compatible with the use of magnetic resonance imaging due to its non-ferromagnetic nature. Nickel ion release after implantation of coils is below the allowable limit. The coil derives its elastic properties from the nitinol wire, and is shaped in a special pre-determined double-loop. The distal and proximal ends of the coil are terminated with a smooth a traumatic ball. To reduce rigidity and lessen pressure of the coil on the airway wall, the diameter of the most proximal end of the coil is smaller than the rest of the coil. The coil is available in various lengths to accommodate different-sized airways. The most common used lengths are 100, 125 and 150 mm. The coil is self-actuating and is delivered straight into an airway and recovers to a non-straight, pre-determined shape upon deployment. Multiple coils need to be placed in different airways to achieve adequate treatment effect.



The step-by-step lung volume reduction coil procedure

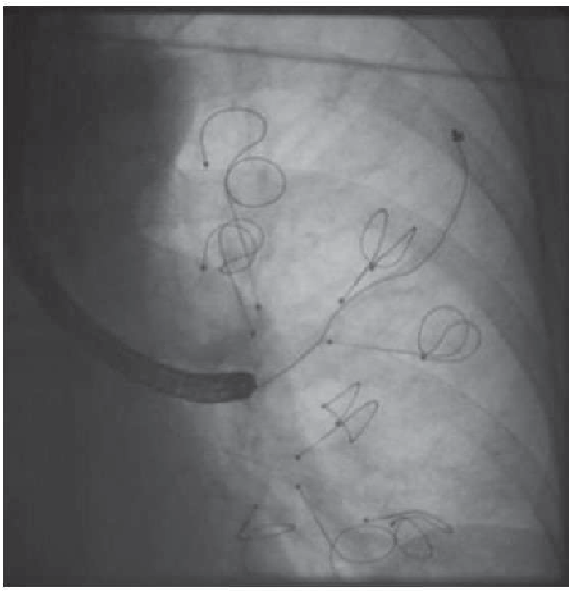
1. Navigate the bronchoscope to the target airway and position at the ostium of a sub segmental airway.
2. Insert both the catheter and guidewire into the working channel of the bronchoscope.
3. Advance and navigate the guidewire into the distal targeted airway (figure 2A) under fluoroscopy guidance; stay minimal 3 cm away from the pleura.
4. Hold the guidewire position fixed relative to the bronchoscope and advance the catheter (figure 2B) distally up to but not past the point where the tip of the catheter is aligned with the tip of the guidewire.
5. Use the radiopaque markers on the guidewire to measure the airway length.
6. Remove the guidewire from the catheter while maintaining the catheter position.
7. The desired size coil can be loaded into the cartridge.
8. Connect the cartridge to the luer-lock hub of the catheter, and lock into place.
9. Deliver the coil into the catheter by advancing the forceps and coil.
10. Align the distal end of the coil with the distal end of the catheter.
11. Position the coil using fluoroscopy (figure 3).
12. Have an assistant hold the bronchoscope fixed relative to the patient.
13. Deploy the coil using fluoroscopy by withdrawing the catheter with one hand, while holding the coil position fixed with the forceps using the other hand.
14. Verify the position of the coil under fluoroscopy and release the coil by unlocking the forceps.
15. Remove the forceps from the catheter (figure 2C & figure 2D).
16. The catheter may continue to be used to repeat steps 3–15 to deploy additional coils. The coil can be removed or repositioned by reversing this implantation process.

Figure 2. Illustrative airway aspect during the lung volume reduction coil procedure.



(A) Bronchoscopic view of the guidewire enters into a segmental airway; (B) The delivery catheter positioned over the guidewire at the entrance of the same airway; (C) Bronchoscopic aspect of the proximal end of a coil sticking out of a subsegmental airway and (D) The biopsy forceps grasping the coils' proximal end to recover it before removing the coil.

Figure 3. Fluoroscopic image during the treatment, showing the distal end of the coil being aligned with the distal end of the catheter position.



Mechanism of action

The lung volume reduction coil is designed to improve the elastic recoil of lung tissue and reduce the airway resistance and hyperinflation in emphysema patients. Furthermore, reduction of the residual volume of the hyperinflated lung improves diaphragmatic function and inspiratory muscle function. The treatment effects are independent of collateral ventilation. The improvement of the lung elastic recoil is still a hypothetical mechanism of action, as no data are currently available to clinically support this. However, based on the nitinol properties of the coil, the lung recoil strength is thought to be significantly improved. Reduction in static hyperinflation is supported by clinical trial observations showing a significant reduction in both residual volume and residual volume/total lung capacity.[24,25] Recently, we also showed that airway resistance significantly improves after lung volume reduction coil treatment.[3,26] It is known from lung volume reduction surgery literature that improvement in static lung volumes also improves diaphragm function. Summarizing the mechanisms of action of the coil might also imply a beneficial effect on diaphragm function. However, to date, there are no supporting data besides incidental chest X-rays showing changes in diaphragm position after treatment.[27] Further research is necessary to learn more about the mechanism of action of the coil.

Clinical profile

The lung volume reduction coil treatment has been evaluated in a few European clinical trials. The RePneu lung volume reduction coil system has consistently demonstrated in animal studies.[28] and clinical studies, the ability to perform safely within the clinical use environment.[24,25] The procedure is safe to perform under general anesthesia. No procedural events occurred. All events that occurred in these studies could be treated with the standard medical treatment. During the procedure, the coil can be removed or repositioned by reversing the implantation process. In clinical practice, it is hardly necessary for any medical reason to remove a coil after the initial treatment. However, when a medical reason occurs (e.g., pleural pain), an individual coil can be removed on condition that the proximal end (ball) of the coil can be recovered with the biopsy forceps. Animal studies confirmed that it is feasible to remove coils within 2 months after implantation.[28]

In 2008, in Germany, a clinical pilot study was performed to primarily evaluate the safety of the first-generation lung volume reduction coil system. Eleven patients with severe heterogeneous (N=3) as well as homogeneous emphysema (N=8) were included according to the inclusion and exclusion criteria of the National Emphysema Treatment Trial. Ten patients underwent two-times and one patient once the lung volume reduction coil treatment. During each procedure, three to six coils were implanted with a procedure time between 20 and 75 minutes. All procedures were performed under general anesthesia, were feasible and well tolerated by the patients. In the follow-up period of at least 7 and up to 11 months, a total of 33 mild-to-moderate adverse events were reported. All events could be treated with the standard medical treatment. Nineteen adverse events (N=10 dyspnea, N=5 coughing, N=3 COPD exacerbations and N=1 chest pain) were reported as possibly related to the device or bronchoscopic procedure. Although this study was not powered to evaluate the statistical significance between patients with heterogeneous and homogeneous emphysema, in this

study, patients with heterogeneous emphysema seem to have better outcomes in lung function parameters, quality of life and exercise. This first study using coils in these severely diseased patients has showed us that the procedure is safe and feasible.[13]

In 2009, in the Netherlands, the second lung volume reduction coil study was performed to evaluate the safety and efficacy of the lung volume reduction coil treatment in patients with a heterogeneous emphysema distribution. Sixteen patients with heterogeneous emphysema were included. In this uncontrolled, open-label trial, the lung volume reduction coil treatment was optimized by increasing the number of coils per lobe from 6 to 10, and using the implantation of a new second-generation coil. Twelve patients underwent bilaterally treatment in two sequential procedures and four patients received the lung volume reduction coil treatment in one lung. During each procedure, a median of 10 (range 5–12) coils were placed with a procedure time of 36.5 (range 20–60) minutes. All procedures were performed under general anesthesia and the lung volume reduction coil procedure was well tolerated by the patients. No adverse events were observed during the lung volume reduction coil procedure. In 28 procedures, one pneumothorax occurred 1 hour after the bronchoscopy. This patient responded within a day to chest tube drainage. During the recovery period, defined as <1 month after each coil procedure, slight hemoptysis (<5 ml in 21 procedures) and transient chest pain (in four procedures) were reported as adverse events, and all these events resolved within a few days after the procedure without medical intervention. In the follow-up period defined as more than 1 month up to 6 months, a total of 14 COPD exacerbations were reported as possibly related to the procedure. All adverse events in this study could be managed with standard medical treatment. At 6 months follow-up after the final treatment, more than 50% of the patients responded better than the minimal clinical important difference for forced expiratory volume in 1 second, distance on 6 minute walk test and the St. George Questionnaire.[29-32] This second study showed us that the lung volume reduction coil treatment has an acceptable safety profile and results in significant improvements in quality of life, lung function and exercise capacity in patients with upper-lobe predominant emphysema.[24]

In 2010, a third lung volume reduction coil study was conducted in the UK. Forty-seven patients with both heterogeneous as well as homogeneous emphysema were included in this prospective, randomized controlled multicenter trial. In the treatment group, 21 patients underwent bilateral lung volume reduction coil treatment and 2 patients a unilateral treatment. The 24 patients who were randomized to the control (usual care) group did not receive the lung volume reduction coil treatment but underwent the same assessments, except the bronchoscopy, as the patients in the treatment group. Both groups were compared after 3 months follow-up after the final treatment. In the bilateral treated patients, a mean number of 18.5 coils (17.1–20.0) were placed with a mean procedure time of 44.9 minutes (range 20–88) per procedure. Six procedures were performed under general anesthesia and 38 procedures were done under deep conscious sedation. In the 44 procedures performed, two pneumothoraces occurred 2 hours after the bronchoscopy. Both patients responded within a day to chest tube drainage. During the recovery period, defined as <1 month after each lung volume reduction procedure, there were two COPD exacerbations and two lower respiratory tract infections in the treatment group and one COPD exacerbation in the usual

care group reported as serious adverse events. All events resolved within 7 days after the procedure. In the follow-up period defined as more than 1 month up to 3 months after final treatment, a total of three COPD exacerbations were reported in the treatment group and two COPD exacerbations and one lower respiratory tract infection were reported as serious adverse events. All adverse events in this study could be managed with standard medical treatment. At 3 months follow-up after the final treatment, a significant number of patients in the treatment group responded to above the minimal clinical important difference: 74% for the distance on 6 minute walk test, 57% for the forced expiratory volume in 1 second and 65% of the patients for the St. George's Respiratory Questionnaire. This third lung volume reduction coil study showed improvement of lung function, exercise capacity and quality of life in the lung volume reduction coil treatment group compared with the usual care group.[25]

In 2011, a fourth lung volume reduction coil study was conducted. Ten patients with homogeneous emphysema were included in this single-arm, open-label study in the Netherlands. All patients received, under general anesthesia, maximally 12 coils in each upper lobe, in two sequential procedures. Tests were performed at baseline and at 6 months. Two COPD exacerbations and one small pneumothorax (which spontaneously resolved without a chest tube) were recorded as serious adverse event. At 6 months, follow-up compared with baseline bilateral coil treatment resulted in a significant improvement in exercise performance, pulmonary function and quality of life. This fourth study showed us that the coil treatment is not limited to patients with heterogeneous emphysema, as patients with homogeneous emphysema can benefit as well.[26]

These four European clinical trials showed that the lung volume reduction coil treatment is safe, feasible and effective in patients with both heterogeneous as well as homogeneous emphysema. Efficacy results of these studies are listed in table 2. Recently data has been published from a European multicenter Feasibility Study of PneumRx's Lung Volume Reduction Coil trial.[33]

Table 2. Efficacy results of the lung volume reduction coil treatment from 4 European clinical trials. Follow up is post 2nd treatment.

	1st study[12] 3 month FU	2nd study[23] 6 month FU	3rd study[24] 3 month FU	4th study[29] 4 month FU
	N=11	N=14	N=23	N=10
FVC	-1.5±6%	+13.4±12.9%	-	+10,0% (-8 to +57)
FEV_1	-5.0±2.9%	+14.9±17%	+14.2% (7 to 22)	+16.6% (-16 to +55)
RV	+3.3±4.6%	-11.4±9.0%	-0.51 Liter (-0.7 to -0.3)	-0.79 Liter (-1.20 to +0.04)
6MWD, %	+5.6±8.5	+32.9±36.5	-	-
6MWD, meter	-	+84±73	+51 (28 to75)	+42 (+15 to +141)
SGRQ	-6.1±4.4	-14.9±12.1	-8.1 (-14 to -2)	-11 (-25 to +6)

Future prospective randomized controlled trial data will have to confirm the efficacy of the lung volume reductioncoil treatment in both heterogeneous and homogeneous populations when compared with usual care. Currently, two larger randomized controlled trials using lung volume reduction coils are underway: RENEW study[22] (N=315) and REVOLENS study[34,35] (N=100).

Current status in the medical field

Lung volume reduction coil treatment is commercially available outside the USA on a large scale. Lung volume reduction coil treatment is not approved by the FDA and is considered investigational in the USA.

Expert commentary & five-year view

Lung volume reduction coil treatment is a novel therapy, independent of collateral flow, for patients with both heterogeneous as well as homogeneous emphysema. The procedure is feasible, and the treatment has an acceptable safety profile. The efficacy results have shown promising improvements in pulmonary function, exercise capacity and quality of life. Randomized controlled trials are underway to confirm these results.

The first 12 months follow-up results of the current multicenter randomized controlled trials are available within 2 years. Depending on the safety and efficacy results from these trials, the lung volume reduction coil treatment can be approved by the FDA, and other health authorities outside the USA will consider approval and reimbursement for this treatment.

Key messages

The lung volume reduction coil treatment is a straightforward and safe procedure to perform.

The lung volume reduction coil treatment has an acceptable safety profile.

The lung volume reduction coil treatment reduces lung volume by compressing the most destructed areas of the lung parenchyma and restores the lung elastic recoil.

The lung volume reduction coil treatment results in an improvement of lung function, exercise performance and quality of life.

The lung volume reduction coil treatment is effective in both upper- and lower-lobe predominant emphysema.

Patients with homogeneous emphysema can benefit from the lung volume reduction coil treatment.

The efficacy of the lung volume reduction coil treatment is independent of collateral flow.

REFERENCES

1. Vestbo J, Hurd SS, Agusti AG, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary.
Am J Respir Crit Care Med 2013;187(4):347-65

2. Viegi G, Pistelli F, Sherrill DL, et al. Definition, epidemiology and natural history of COPD.
Eur Respir J 2007;30(5): 993-1013

3. Baraldo S, Turato G, Saetta M. Pathophysiology of the small airways in chronic obstructive pulmonary disease. Respiration 2012;84(2):89-97

4. Cooper CB. Airflow obstruction and exercise. Respir Med 2009;103(3):325-34

5. Russell RE. Chronic obstructive pulmonary disease: getting it right. Does optimal management of chronic obstructive pulmonary disease alter disease progression and improve survival?
Curr Opin Pulm Med 2014;20(2):127-31

6. Fishman A, Martinez F, Naunheim K, et al. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. N Engl J Med 2003;348(21):2059-73

7. Cardoso PF, Snell GI, Hopkins P, et al. Clinical application of airway bypass with paclitaxel-eluting stents: early results. J Thorac Cardiovasc Surg 2007;134(4):974-81

8. Shah PL, Slebos DJ, et al. Bronchoscopic lung-volume reduction with Exhale airway stents for emphysema (EASE trial): randomized, sham-controlled, multicentre trial. Lancet 2011;378(9795): 997-1005

9. Kramer MR, Refaely Y, Maimon N, et al. Bilateral endoscopic sealant lung volume reduction therapy for advanced emphysema. Chest 2012;142(5):1111-17

10. Herth FJ, Gompelmann D, Stanzel F, et al. Treatment of advanced emphysema with emphysematous lung sealant (AeriSeal(R)). Respiration 2011;82(1):36-45

11. Herth FJ, Eberhardt R, Ingenito EP, Gompelmann D. Assessment of a novel lung sealant for performing endoscopic volume reduction therapy in patients with advanced emphysema.
Expert Rev Med Devices 2011;8(3):307-12

12. AeriSeal System for HyperInflation Reduction in Emphysema (ASPIRE trial). ClinicalTrials.gov Identifier. Available from: http://data.linkedct.org/resource/trial/nct01449292

13. Herth FJ, Eberhard R, Gompelmann D, et al. Bronchoscopic lung volume reduction with a dedicated coil: a clinical pilot study. Ther Adv Respir Dis 2010;4(4):225-31

14. Snell G, Herth FJ, Hopkins P, et al. Bronchoscopic thermal vapour ablation therapy in the management of heterogeneous emphysema. Eur Respir J 2012;39(6):1326-33

15. Sciurba FC, Ernst A, Herth FJ, et al. A randomized study of endobronchial valves for advanced emphysema. N Engl J Med 2010;363(13):1233-44

16. Herth FJ, Eberhardt R, Gompelmann D, et al. Radiological and clinical outcomes of using chartis to plan endobronchial valve treatment. Eur Respir J 2013;41(2):302-8

17. Sterman DH, Mehta AC, Wood DE, et al. A multicenter pilot study of a bronchial valve for the treatment of severe emphysema. Respiration 2010;79(3):222-33

18. Ninane V, Geltner C, Bezzi M, et al. Multicentre European study for the treatment of advanced emphysema with bronchial valves. Eur Respir J 2012;39(6):1319-25

19. Eberhardt R, Gompelmann D, Schuhmann M, et al. Complete unilateral vs partial bilateral endoscopic lung volume reduction in patients with bilateral lung emphysema. Chest 2012;142(4):900-8

20. Snell GI, Hopkins P, Westall G, et al. A feasibility and safety study of bronchoscopic thermal vapor ablation: a novel emphysema therapy. Ann Thorac Surg 2009;88(6):1993-8

21. Duerig TW, Pelton AR, Stockel D. The utility of superelasticity in medicine. Biomed Mater Eng 1996;6(4):255-66

22. Lung Volume Reduction Coil Treatment in Patients With Emphysema (RENEW Study). ClinicalTrials.gov Identifier. http://my.clevelandclinic.org/research/clinical_trials/NCT01608490

23. Shabalovskaya SA. Surface, corrosion and biocompatibility aspects of Nitinol as an implant material. Biomed Mater Eng 2002; 12(1):69-109

24. Slebos DJ, Klooster K, Ernst A, et al. Bronchoscopic lung volume reduction coil treatment of patients with severe heterogeneous emphysema. Chest 2012; 142(3):574-82

25. Shah PL, Zoumot Z, Singh S, et al. Endobronchial coils for the treatment of severe emphysema with hyperinflation (RESET): a randomized controlled trial. Lancet Respir Med 2013;1(3):233-40

26. Klooster K, Hacken ten NH, Franz I, et al. Lung Volume Reduction Coil treatment in COPD patients with homogeneous emphysema: a prospective feasibility trial. Respiration 2014;88:116-25.

27. Hamnegard CH, Polkey MI, Thylen A, et al. Effect of lung volume reduction surgery for emphysema on diaphragm function. Respir Physiol Neurobiol 2006; 150(2-3):182-90

28. Ost DE, Boutillette MP, Slebos DJ, Lehrberg DB. Evaluation of the removability of the Lung Volume Reduction Coil. Am J Respir Crit Care Med 2012;185:A5352

29. Holland AE, Hill CJ, et al. Updating the minimal important difference for six-minute walk distance in patients with chronic obstructive pulmonary disease. Arch Phys Med Rehabil 2010;91(2):221-5

30. Hartman JE, Ten Hacken NH, Klooster K, et al. The minimal important difference for residual volume in patients with severe emphysema. Eur Respir J 2012;40(5): 1137-41

31. Jones PW. St. George's respiratory questionnaire: MCID. COPD 2005;2(1): 75-9

32. Puhan MA, Chandra D, Mosenifar Z, et al. The minimal important difference of exercise tests in severe COPD. Eur Respir J 2011;37(4):784-90

33. Deslee G, Klooster K, Hetzel M, et al. Lung volume reduction coil treatment for patients with severe emphysema: a European multicentre trial. Thorax 2014;69:980-6

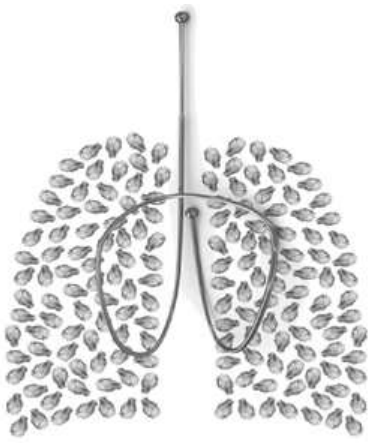
34. Lung Volume Reduction Coil Treatment in Emphysema (STICREVOLENS).
Available from: http://clinicaltrials.gov/show/ NCT01822795

35. Deslee G, Barbe C, Bourdin A, et al. Cost-effectiveness of lung volume reduction coil treatment in emphysema. STIC REVOLENS. Rev Mal Respir 2012;29(9): 1157-64

36. Pulmonx Endobronchial Valves Used in Treatment of Emphysema (LIBERATE Study).
Available from: http://clinicaltrials. gov/show/NCT01796392

37. Evaluation of the IBV valve for emphysema to improve lung function (EMPROVE).
Available from: http://clinicaltrials.gov/show/NCT01812447

38. Sequential segmental treatment of emphysema with upper lobe predominance (STEP-UP) study.
Available from: http://clinicaltrials.gov/ct2/show/NCT01719263



CHAPTER

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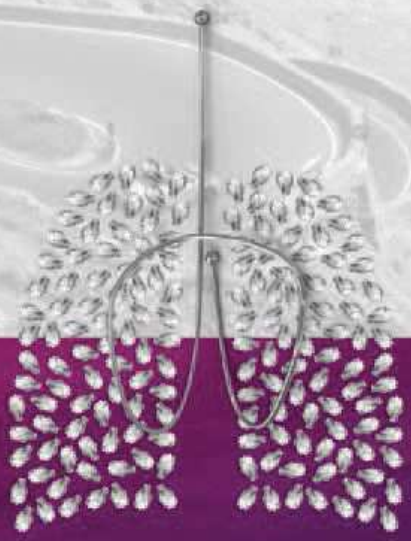


Summary

Summary

The current treatment of COPD offers only limited benefit to patients with severe COPD. A very small subset of these COPD patients will benefit from either lung transplantation or lung volume reduction surgery, but these treatments are highly invasive, scarcely available, and expensive. Therefore, less invasive procedures for lung volume reduction have been developed. In this thesis we investigated two novel bronchoscopic treatments in patients with advanced emphysema; endobronchial valve treatment and lung volume reduction coil treatment.

In **chapter 2** we provide an endoscopic visualization of the rather impressive tissue destruction in the lung parenchyma of a patient with severe emphysema. The alveoli and blood vessels are damaged, and therefore gas exchange is very limited. Furthermore, the lung parenchyma destruction leads to increased tissue elasticity, eventually resulting in increased airway collapse during exhalation, airtrapping and hyperinflation.

In chapter 3 a review (in Dutch) is presented on the current status of bronchoscopic interventions in patients with severe COPD. The review critically appraises the available published data of the coil treatment and endobronchial valve treatment. A case report was added to demonstrate one of our patients who received endobronchial valve treatment. This review was written for a general medical- and non-medical audience to promote, and to better understand these new treatment options for our patients with severe COPD.

In **chapter 4** the results are shown of a study on the role of dynamic hyperinflation in patients with severe COPD. In this study we investigated the feasibility of the manually paced tachypnea test sitting at rest, in 74 patients with severe COPD. We determined the relationship between dynamic hyperinflation and exercise capacity, assessed by the 6 minute walk test. The manually paced tachypnea test was well tolerated in all patients and succeeded to induce dynamic hyperinflation. Multiple regression analysis showed that not dynamic hyperinflation, but static hyperinflation was the most important independent predictor of exercise capacity in this group of patients with very severe COPD.

In **chapter 5** the data of the randomized controlled STELVIO trial is presented. In this study we examined the effectiveness of the endobronchial valve treatment in patients with severe emphysema in whom the absence of collateral ventilation was proven by the Chartis system. Sixty-eight patients 46 female, (mean ± standard deviation age 59±9 years, FEV_1 29±7% of predicted value, forced vital capacity 77±18% of predicted value, and distance on 6 minute walk test 374±86 meter) were randomized to endobronchial valve treatment (N=34) or standard medical care (control group) (N=34). At 6 months, intention-to-treat analyses showed significant between-group differences in favor of the endobronchial valve group in change of FEV_1:+140 ml (95%CI; 55 to 225), forced vital capacity: +347 ml (95%CI; 107 to 588) and in distance on 6 minute walk test +74 meter (95%CI; 47 to 100). By 6 months, 23 serious adverse events were reported in the endobronchial valve group compared to 5 in the control group (P<0.001). One death occurred in the endobronchial valve group. Serious treatment-related adverse events in this group included pneumothorax (18% of patients)

and events requiring valve replacement (12%) or valve removal (15%). This study showed that endobronchial valve treatment resulted in both statistically and clinically significant improvements in pulmonary function, exercise capacity, and quality of life in a selected group of patients with severe emphysema without collateral ventilation. Adverse events needing careful attention did occur, but were manageable.

In the study described in **chapter 6** we investigated the impact of endobronchial valve treatment on physical activity in patients with severe emphysema. 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. Forty-three patients (77% female, age 59±9 years, FEV_1 30±7% of 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 improved significantly compared to the controls in steps/day (+1252 versus -148). A greater increase in steps per day was significantly associated with a stronger decrease in residual volume (r=-0.48) and a greater increase in FEV_1 (r=0.41) and in distance on 6 minute walk test (r=0.50). In this study we were able to demonstrate that daily physical activity significantly improved 6 months after bronchoscopic lung volume reduction treatment using endobronchial valves. This improvement was without any specific intervention or encouragement on physical activity.

In **chapters 7, 8, 9** and **10** the development of another new experimental device is shown. In these studies we investigated the bronchoscopic lung volume reduction coil treatment. The first study (**chapter 7**) was a prospective single centre pilot study investigating the feasibility, safety, and efficacy of the coil treatment, specifically in patients with severe heterogeneous emphysema. In this first in human study, 16 patients (baseline FEV_1, 28±8% of predicted value) were treated bronchoscopically with coils under fluoroscopic guidance in 2 sequential procedures. Four patients were treated in 1 lung, and 12 patients were treated in both lungs. A median of 10 (5-12) coils was placed per lung. Adverse events possibly related to either the device or the procedure within 30 days after treatment were pneumothorax (N=1), pneumonia (N=2), COPD exacerbation (N=6), chest pain (N=4), and mild hemoptysis (N=21). From 30 days to 6 months, the adverse events that occurred were pneumonia (N=3) and COPD exacerbation (N=14). All events resolved with standard care. Six months after LVR-coil treatment, there were significant improvements in (mean ± standard deviation) SGRQ, -15±12 points, FEV_1, +15±17%, forced vital capacity, +13±13%, residual volume, -11±9% and distance on 6 minute walk test +84±73 meter (all $P<0.005$). This study showed that lung volume reduction coil treatment is technically feasible with an acceptable safety profile. We concluded that the lung volume reduction coil treatment is a promising technique for the treatment of patients with severe heterogeneous emphysema.

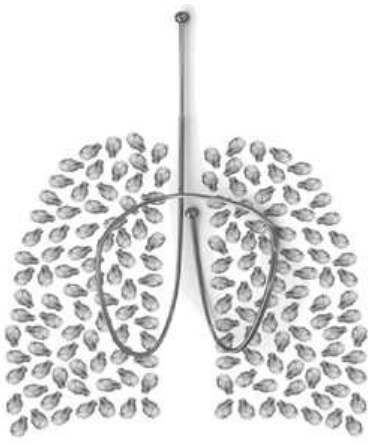
Following the early experiences of the lung volume reduction coil treatment, we further investigated the feasibility, safety and efficacy of lung volume reduction coil treatment in a multicentre study in a larger group of patients with severe emphysema. **Chapter 8** was based on data of this prospective open-label trial, which was conducted in 11 European hospitals. Sixty patients (61±8 years, FEV_1, 30±6% of predicted value) were bronchoscopically treated with coils (55 bilateral, 5 unilateral), with a median of 10 (range 5–15) coils per lobe. Within 30 days post-treatment, 7 COPD exacerbations (6%), 6 pneumonias (5%), 4 pneumothoraces (4%) and 1 hemoptysis (1%) occurred. At 6 and 12 months, respectively, change in SGRQ was −12±13 points and −11±13 points, change in distance on 6 minute walk test was +30±74 meter and +51±76 meter, change in FEV_1 was +0.11±0.20 Liter and +0.11±0.30 Liter, and change in residual volume was −0.65±0.90 Liter and −0.71±0.81 Liter (all $P<0.01$). Post-hoc analyses showed significant improvements in SGRQ, 6 minute walking distance and residual volume in patients with both heterogeneous and homogeneous emphysema. This study confirmed our single center open-label study (Chapter 7), showing that lung volume reduction coil treatment results in significant clinical improvements in patients with severe emphysema, with a good safety profile and sustained results for up to 1 year after treatment.

Lung volume reduction coil treatment was shown to be safe and clinically effective in patients with severe emphysema in the short term; however, long-term safety and effectiveness had not been evaluated. Therefore in **Chapter 9**, we further investigated the long-term safety and effectiveness of lung volume reduction coil treatment in patients with severe emphysema. Thirty-eight patients with severe emphysema (median age 59 years, FEV_1 27% of predicted value), who were treated in two previous lung volume reduction coil clinical trials, were invited for a voluntary annual visit. Thirty-five patients visited the hospital 1 year, 27 patients 2 years and 22 patients 3 years following coil placement. No coil migrations were observed on X-ray. At 1-year follow-up, all clinical outcomes significantly improved compared with baseline. At 2 years, residual volume, mMRC score and the SGRQ score were still significantly improved. At 3 years, a significant improvement in mMRC score remained, and 40% of the patients reached the minimal important difference in distance on 6 minute walk test, and 59% in the SGRQ. We concluded that at 3-year follow-up, the lung volume reduction coil treatment showed no long-term unexpected adverse and device-related events.

Lung volume reduction coil treatment has been shown to be effective in patients with heterogeneous emphysema, and our post-hoc results showed a strong signal for efficacy in homogeneous patients as well, but this treatment had not been prospectively investigated in patients with homogeneous emphysema. **In chapter 10** a study is presented that investigated the lung volume reduction coil treatment in severe emphysema patients with a homogeneous emphysema distribution. In this single-arm, open-label study, 10 patients with severe airway obstruction and hyperinflation were treated with a maximum of 12 coils in each upper lobe in 2 sequential procedures. A median of 11 (range 10–12) coils were placed in each lung. Two COPD exacerbations and 1 minor pneumothorax were recorded as serious adverse events. At 6 months, the distance on 6 minute walk test improved from 289 to 350 meter (P=0.005); forced vital capacity from 2.17 to 2.55 Liter (P=0.047); residual volume from 5.04 to 4.44 Liter (P=0.007) and SGRQ score from 63 to 48 points (P=0.028).

This study showed that the benefit of lung volume reduction coil treatment is not limited to patients with heterogeneous emphysema, but that patients with homogeneous emphysema benefit as well.

In **chapter 11** the evolution of the lung volume reduction coil technology and its current status are reviewed. Lung volume reduction coil treatment is a novel therapy, independent of collateral flow, for patients with both heterogeneous as well as homogeneous emphysema. The procedure is feasible, and the treatment has an acceptable safety profile in experienced hands. The efficacy results have shown promising improvements in pulmonary function, exercise capacity and quality of life. Future prospective randomized controlled trial data will have to confirm the efficacy of the lung volume reduction coil treatment in both heterogeneous and homogeneous populations when compared with usual care.



CHAPTER

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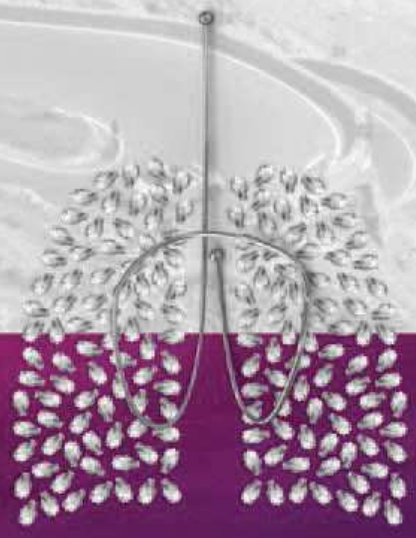


Discussion and future perspectives

Discussion

The key message of this thesis is that bronchoscopic treatment with endobronchial valves in selected patients with emphysema significantly improves pulmonary function, exercise capacity, and quality of life. The endobronchial valve treatment can be considered as an additional treatment option next to optimal conventional medical treatment for patients with COPD and with very severe emphysema preselected to have proven absence of interlobar collateral ventilation. For patients who are not qualified for endobronchial valve treatment the coil-treatment has been shown to be a valid treatment option. However, its real efficacy and safety profile needs to be further evaluated in randomized controlled trials with larger sample sizes and longer follow-up.

For patients with very severe COPD, who are on optimal medical treatment, additional surgical treatments can be considered. Lung transplantation is one, but its availability is very limited due to the scarcity of donor lungs, and also patients are not allowed to have major co-morbidities or other surgical restrictions. Lung volume reduction surgery is also an effective treatment, but only in a very small group of carefully selected patients. Further investigation is necessary to establish how bronchoscopic intervention should be positioned relative to lung volume reduction surgery and lung transplantation. We postulate that bronchoscopic lung volume reduction can act as a bridge to one of the surgical interventions in some, and as an alternative cheaper, and more accessible option in other patients with advanced emphysema.

Endobronchial valve treatment

In the STELVIO trial we demonstrated that endobronchial valve treatment significantly improved lung function, exercise capacity, and quality of life compared to usual care. In this prospective randomized controlled trial the earlier published open label and post-hoc best responder profile of endobronchial valve treatment was confirmed. In our trial, patients were pre-selected on having complete- or near complete fissures on HRCT scan, after which an additional 15% of the patients for endobronchial valve treatment were excluded by Chartis assessment because of collateral ventilation. We previously reported that these collateral ventilation-positive patients would not benefit from the endobronchial valve treatment.[1] A recently published study, the BeLieVeR HIFi study[2], also showed that patients with intact interlobar fissures on CT scan but with presence of collateral ventilation measured with the Chartis system did not experience benefit from endobronchial valve treatment. Therefore, endobronchial valve treatment in selected patients with very severe emphysema and with proven absence of interlobar collateral ventilation should be considered as an additional treatment option besides the conventional treatment. This accurate selection of patients is in our opinion a perfect example of personalized or precision medicine.

Effective therapies are never without side effects. Pneumothorax was the most frequently occurring adverse event. The occurrence is commonly thought to be due to the rapid shift in lung volumes causing rupture of a bleb/bullae either due to barotrauma, or due to pleural adhesions. Because a pneumothorax potentially is a life threatening complication

in severe emphysema, close monitoring of patients after endobronchial valve treatment is crucial. In the STELVIO trial the median hospital stay after treatment was one day. In our clinical practice today we have expanded the inpatient hospital stay to at least five nights after endobronchial valve treatment to monitor for the occurrence of life threatening pneumothorax. Furthermore, pneumothorax may also occur in a later phase.[3,4] and therefore patients need to be provided with clear instructions also after discharge.

Repeated bronchoscopy is sometimes necessary to either replace temporarily or remove permanently the endobronchial valves. Reasons to do so include loss of initial lung volume reduction due to formation of granulation tissue leading to leakage or valve migration. Previous studies postulated that endobronchial valve treatment is fully reversible and does not preclude future therapeutic options. Our study confirms this opinion, since all patients in whom endobronchial valves were removed recovered without further side effects.[5,6,7]

The data of our study showed that the endobronchial valve treatment is effective up to 6 months. Two small uncontrolled case-series have now shown sustained improvements up to two years after endobronchial valve treatment.[8,9] Where for lung volume reduction surgery long term survival benefit and improved exercise capacity has been demonstrated in selected patients[10], for endobronchial valve treatment, long-term effectiveness still needs to be proven.

Lung volume reduction coil treatment

The second aim of the thesis was to investigate the feasibility and efficacy of a new experimental treatment, the placement of coils in patients with severe emphysema. In 3 sequential studies we showed that this coil treatment is a promising technique both in patients with heterogeneous- as well as homogeneous emphysema. The treatment is technically feasible and results in significant improvements in pulmonary function, exercise capacity, and quality of life with sustained results at 1 year. However, in our very first ever treated patients with coils, the clinical benefit gradually declined over a 3 year period. The coil treatment has an acceptable safety profile without long-term unexpected device related adverse events.

Serious adverse events mainly occurred in the first 30 days after the procedure. The total rate of these events following endoscopic implants did not exceed the number of exacerbations and pneumonias that were reported in the sham-control bronchoscopy group of the EASE trial.[11] Lung volume reduction coil procedure related events that occur are typically very mild hemoptysis or mild chest discomfort, both for a few days and requiring no intervention. In our studies reported here, we encountered no deaths or coil related consolidations, but these did occur in other studies.

In our study, broad selection criteria were purposely used in order to evaluate the effectiveness in a population of patients representative of the patients we see in daily practice. We hypothesized that this may be one of the reasons for the large variability of response between patients. However, a significant responder rate of approximately 50-60%

was found for several clinical endpoints. To better understand the predictors of response to lung volume reduction coil treatment, we conducted a multivariate analysis to assess the relationship between the response to treatment and baseline variables typically identified as predictors of outcome, such as hyperinflation and emphysema heterogeneity. Using the 6 month endpoints, none of the evaluated baseline variables provided a meaningful predictor of response to lung volume reduction coil treatment. Other potential variables could include more nuanced emphysema phenotypes beyond heterogeneous or homogeneous classification, such as the presence of small airways disease, and variability in coil placement strategies such as exact position, length and number of coils used. A recently published meta-analysis using all raw lung volume reduction coil trial data in a larger patient cohort (N=140) identified higher residual volume at baseline as the only independent predictor of treatment succes.[12]

When comparing the results for patients with upper lobe versus lower lobe lung volume reduction coil treatment, a trend in the outcome differences was observed in favor for upper lobe treatments.[12] However, to date only a small number of patients has been treated in the lower-lobes, and the lower FEV_1 results seen with lower lobe coil treatments is comparable to the experience with lung volume reduction surgery in the lower lobes where the effect on improving FEV_1 is also limited compared with other outcome variables.[13] However, in general the FEV_1 shows a weak association with exercise performance in patients with severe emphysema.[14] Future research is needed to evaluate whether, as currently hypothesized, the much bigger lower lobes require a greater number of coils to optimize results.

Lung volume reduction coil treatment proved efficacious both in patients with heterogeneous and with homogeneous. The primary mechanism of action of coils appears to be mechanical re-tensioning of the lung matrix, rather than just reducing absolute lung volume alone. In the studies reported in this thesis, we observed a significant decrease in airway resistance after lung volume reduction coil treatment. Beforehand, one might expect that implantation of coils inside the airways would obstruct airflow and increase airway resistance. Apparently, the mechanical properties of the lung are improved by the treatment and, importantly, our study also suggests that the lung parenchyma in subjects with homogeneous emphysema is still healthy enough to transfer the elastic recoil forces to the airways. Despite this interesting observation, additional studies are necessary to better characterize the mechanisms of action of the coil treatment, and thereby to better identify responders to coil treatment. Furthermore, future research needs to confirm the efficacy of the coil treatment in homogeneous emphysema, which represents a large number of patients usually excluded from other surgical and bronchoscopic lung volume reduction treatment options.

The lung volume reduction coil trials presented in this thesis were uncontrolled studies and therefore susceptible to potential bias. However, we have previously shown that even in a sham controlled bronchoscopic interventional trial design, only a small placebo effect was observed in patients with severe COPD.[11] Nevertheless, one of the next steps should be to confirm the results in a prospective, multicenter, randomized, controlled study to compare efficacy outcomes between the coil treatment and standard of care. The results

of a French N=100 patient's multicenter 1:1 randomized study comparing coils with usual care were recently published. At 6 months, lung volume reduction coil treatment was associated with a significant decrease in hyperinflation and sustained improvement in quality of life.[15] Another study (called RENEW) is being conducted since December 2012. The first brief preliminary results of this N=315 patient's multicenter randomized controlled trial were made public in December 2015 by the study sponsor PneumRx/BTG. All primary and secondary endpoints of the study were met. Analysis showed statistically significantly greater improvements in the treatment group than in the control group from baseline to 12 months: the increase in the distance on 6 minute walk test was greater by 10.2 meter (P=0.015), the increase in FEV_1 was greater by 8.8% (P < 0.0001). Improvements were also seen in SGRQ scores with a -8.9 points greater reduction in the treatment group than in the control group (P<0.0001). Serious adverse events associated with bronchoscopy and coil placement such as pneumothorax, lower respiratory tract infections, respiratory failure, hemoptysis, COPD exacerbation, and dyspnea occurred at a higher rate in the treatment arm, as anticipated.

Role of dynamic hyperinflation

The final aim of this thesis was to determine the role of dynamic hyperinflation in patients with severe COPD. We assessed whether the manually paced tachypnea test, sitting at rest, is feasible also in patients with severe COPD, and whether the induced dynamic hyperinflation correlates with exercise performance in these patients. We indeed demonstrated good feasibility for the use of the manually paced tachypnea test to induce dynamic hyperinflation in a group of patients with severe COPD. Static hyperinflation in this severe group seemed to be to be a better predictor of exercise performance than dynamic hyperinflation. We believe that the observed negative association between dynamic hyperinflation and exercise capacity is attributable to the more severe disease state of our patient population. All the patients in our study were referred and evaluated for bronchoscopic lung volume reduction treatment and were diagnosed with severe static hyperinflation. Additionally, it would be interesting to also investigate dynamic hyperinflation after a bronchoscopic treatment; our studies demonstrated that static hyperinflation decreases after successful bronchoscopic lung volume reduction treatment.

Patient selection for bronchoscopic lung volume reduction treatment

We have shown that bronchoscopic lung volume reduction can be an additional treatment option for patients with advanced emphysema. Nevertheless, pharmacological treatment, pulmonary rehabilitation, as well as smoking cessation remain the basis of treatment for COPD. When a patient with advanced emphysema still experiences severe complaints despite optimal medical management, a bronchoscopic lung volume reduction treatment can be considered. From previous trials we have learned that patient selection is paramount for correctly identifying candidates who will benefit from a bronchoscopic lung volume reduction treatment. In other words: not every patient with severe COPD is suitable. For example, a patient with a predominant chronic bronchitis phenotype of COPD is not suitable for lung volume reduction treatment.

Therefore, a stepwise approach is needed to evaluate the most suitable treatment option for the individual patient.

Our approach is to carefully evaluate each individual patient, and use at least information about:

- Burden of the disease and motivation to contribute to improvement
- Presence of co-morbidity
- Severity of airway obstruction and hyperinflation
- Radiological assessment of emphysema and fissure integrity

Burden of the disease and motivation to contribute to improvement

A patient with advanced emphysema should have severe complaints despite optimal medical management, and experience poor quality of life and reduced exercise performance, to be selected for bronchoscopic treatment. Also patients who are highly motivated to improve their health status and are trying to keep as physically active as possible, and follow a supervised exercise program before the intervention are potential candidates.

Presence of co-morbidity

Patients with co-morbidities, such as severe pulmonary hypertension, significant heart failure, or severe chronic respiratory failure are not eligible for a bronchoscopic lung volume reduction treatment. The bronchoscopic interventions are performed under either deep conscious sedation or general anesthesia, and the treatments do not come without adverse events. Patients will have to be fit enough to sustain the procedure and to survive adverse events. Also significant co-morbidity can contribute notably to the patient's symptoms in such a way that a bronchoscopic treatment does not relieve these. Furthermore, patients with repeated infections of the lower airways and frequent exacerbations of COPD, are not eligible for treatment. Foreign, blocking material can induce even more infections. It is important to note that a bronchoscopic lung volume reduction treatment is only suitable for patients in a stable disease phase, thus it cannot be advised to be used as an emergency treatment.

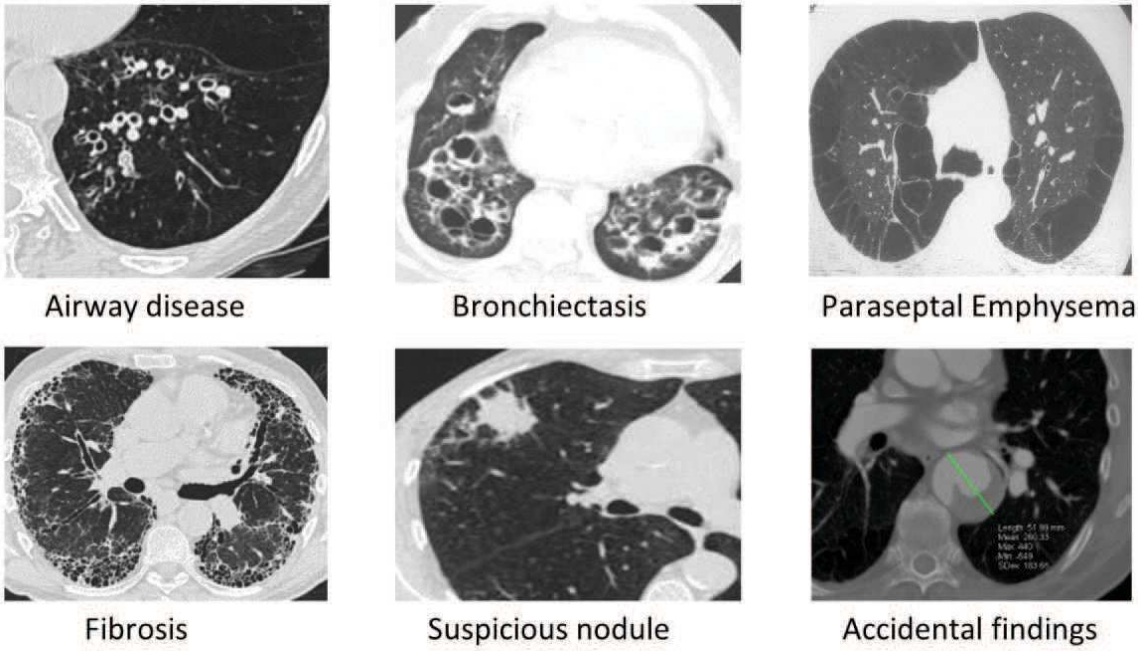
Severity of airway obstruction and hyperinflation

There is no full consensus on criteria for lung function. To be eligible for many of the bronchoscopic lung volume reduction studies performed so far, patients needed an FEV_1 between 15% and 45% of predicted, which is also what we adhere to. Additionally patients should have significant hyperinflation as measured by bodyplethysmography. The residual volume should be above 175% of predicted and the total lung capacity above 100% of predicted. Preferably also the residual volume/total lung capacity ratio should be above 55%.

Radiological appearance of emphysema

A thin slice (≤1mm) volume CT scan (without contrast) is absolutely required in the selection procedure for bronchoscopic lung volume reduction. First a primary assessment should be performed to ensure the absence of abnormalities such as significant airway disease

(bronchial wall thickening, bronchopathy, bronchiectasis), paraseptal emphysema, lung fibrosis, or a suspicious nodule. When these findings appear, the patient is not eligible for a lung volume reduction treatment even when the pulmonary function shows eligibility. The figure below presents examples of abnormalities in the lung disqualifying the patient for bronchoscopic lung volume reduction treatment.



In case there are no significant abnormalities deteced on the HRCT an assessment should be performed to characterize the emphysema and to evaluate the distribution (homogeneous or heterogeneous) and the percentage of parenchymal destruction expressed as the proportion of pixels. Patients with a parenchymal destruction less than 50% in the potential treatment target are not suitable for endobronchial valve treatment or lungvolume reduction surgery. Patients with a parenchymal destruction more than 75% are not suitable for coil treatment (See figure “Overview of a quantitative emphysema score” in the introduction section of this thesis).

Finally, fissure integrity should be assessed, since this will guide the appropriate treatment option. The exact radiological completeness of the lobar fissure necessary for an effective treatment is not well known. The current data indicates that valve treatment is not effective if the interlobar fissure between the treatment target lobe and adjacent lobe is less than 85-90%, because of the high probability of presence of collateral ventilation. Patients with an incomplete fissure should not be considered for treatment with endobronchial valves but may be eligble for lung volume reduction coil treatment.[16]

If the interlobar fissure between the treatment target lobe and adjacent lobe is more than 85% intact, the absence of collateral ventilation can be confirmed by measurement of collateral ventilation with the Chartis system. When using this combined approach of assessment of fissure integrity on CT and the Chartis measurement, a responder rate of approximately 75% can be achieved.[17]

Summary of patient selection for bronchoscopic lung volume reduction treatments

A summary of the current main inclusion and exclusion for lung volume reduction treatments in our hospital is presented in the following figure. Patients who fulfill these inclusion and exclusion criteria could be presented to a multidisciplinary team including a radiologist, pulmonologist and interventional pulmonologist. In this team the pro and cons of the various treatment options should be discussed, like a wait and see approach, endoscopic lung volume reduction, lung volume reduction surgery and lung transplantation. Importantly, future lung transplantation is not a contraindication for bronchoscopic lung volume reduction.[18]

INCLUSION

Diagnosed with COPD
- Emphysema phenotype
- Symptomatic (mMRC>1)

Medical treatment
- Optimal pharmacological treatment
- Post-rehabilitation and/or maintenance (supervised) physical activity
- Stopped smoking for at least 6 months
- Vaccination
- Optimal nutrition

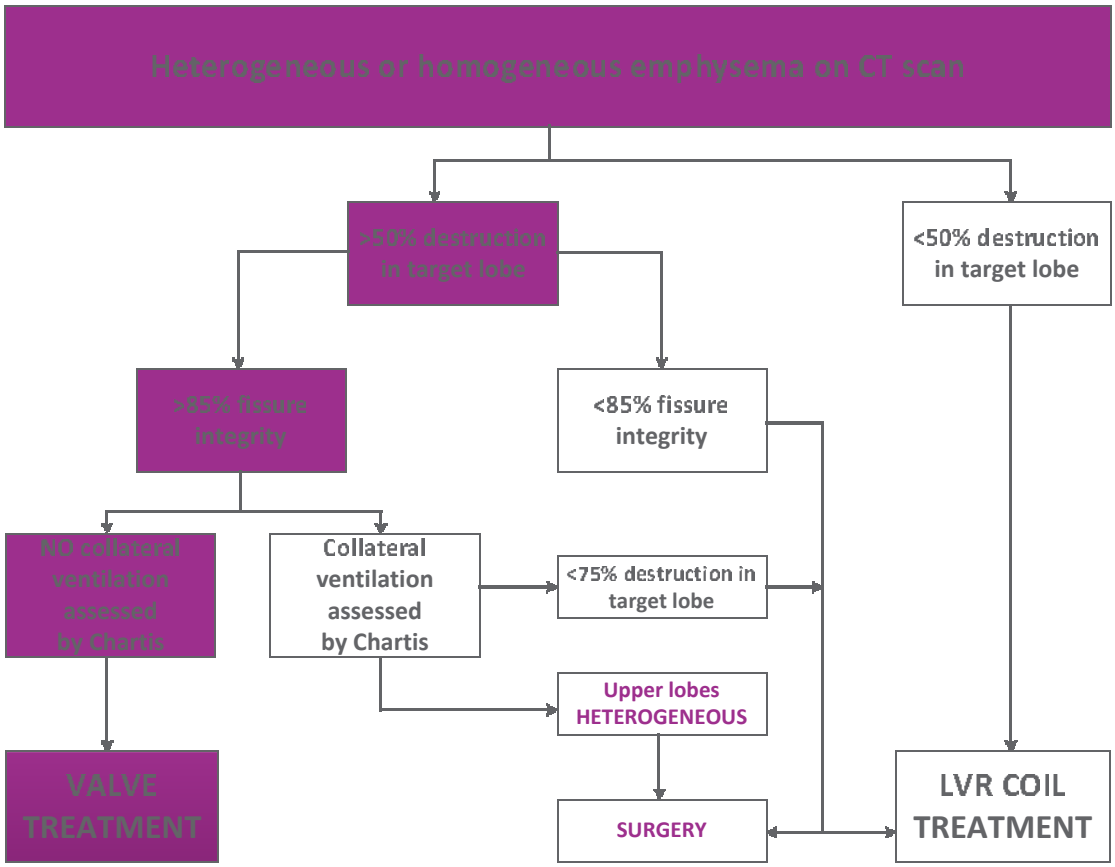
Pulmonary function testing
- FEV_1 % predicted between 15% and 45%
- Residual volume % predicted >175%
- Total lung capacity % predicted >100%
- Residual volume/total lung capacity >55%

EXCLUSION

- Chronic bronchitis phenotype
- Clinically significant bronchiectasis
- Frequent exacerbations
- Previous lobectomy, pneumonectomy, lung volume reduction surgery or lung transplantation
- Significant abnormalities on CT scan, such as severe paraseptal emphysema, fibrosis and suspicious nodule
- Severe hypercapnia ($PaCO_2$>8kPa)
- Severe hypoxia (PaO_2 <6.0kPa)
- Pulmonary hypertension (right ventricle systolic pressure >50 mmHg)
- Heart failure (left ventricle ejection fraction <40%)
- Maintenance anticoagulation: coumarines, low molecular weight heparin, clopidrogel or similar antiplatet agents, direct thrombin inhibitors

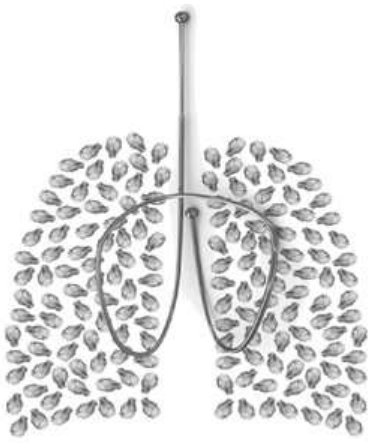
'The Groningen' treatment algorithm

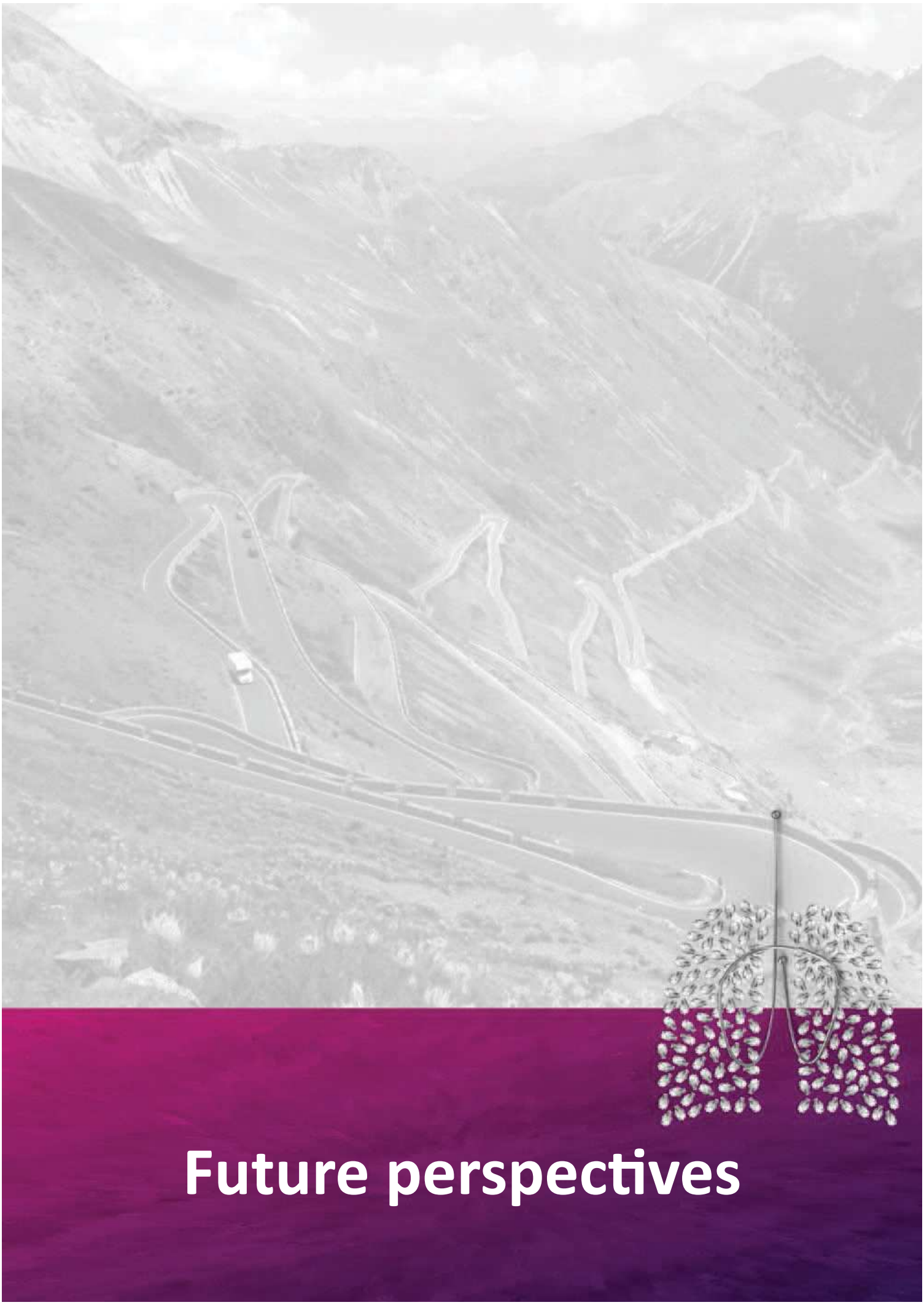
The treatment algorithm shown in the following figure shows the different treatment options for patients fulfilling the described inclusion and exclusion criteria.



Choice of treatment depends on the severity of parenchymal destruction, fissure integrity (both performed by visually assessment) and presence or absence of collateral ventilation confirmed with the Chartis system. Nevertheless, when taking these steps together, the final treatment recommendation is personalized medicine in these patients with severe emphysema. Other factors such as the severity of hyperinflation and the degree of heterogeneity can further influence the choice of treatment. The algorithm is a guidance to treatment which is based on the available literature and experiences from our hospital.

Currently, only lung volume reduction surgery and endobronchial valve treatment have reached the evidence level to be used outside clinical trials. For these techniques, as well as for the not fully proven newer techniques, keeping good registries in limited centers employing the technique is probably wise in order to ensure enough number of interventions with excellent expertise, to expand the evidence base, and to support and guide the reimbursement process of these therapies.





Future perspectives

Future perspectives

In this thesis new treatment modalities for patients with severe emphysema were investigated, however, there are still many challenges for future research.

Pneumothorax associated with endobronchial valve treatment

The important benefit of bronchoscopic lung volume reduction using endobronchial valves, comes with a significant risk of a pneumothorax. In approximately one out of four patients treated with endobronchial valves a pneumothorax occurred. In patients with severe emphysema a pneumothorax potentially is a life threatening complication and needs close monitoring of patients after endobronchial valve treatment. The occurrence is commonly thought to be due to the rapid shift in lung volumes causing rupture of a bleb/bullae either due to barotrauma, or due to pleural adhesions.[4]

The presence of pleural adhesions in the target lobe on CT scan might provide prognostic information about likelihood of future pneumothorax occurrence, and this can be assessed on existing scans of patients prior to having had a procedure. Furthermore, strenuous activity or coughing might also lead to higher risk of pneumothoraces.[19] To decrease the pneumothorax incidence it might be useful to modify post-treatment medical care to include bed rest for 48 hours and provide cough suppression after bronchoscopic lung volume reduction with valves. However, probably this will not prevent pneumothoraces in a later phase.[20] Future research will certainly increase our knowledge on pneumothorax occurrence. A prospective, randomized study will be needed to confirm if modified post-treatment medical care, perhaps especially in higher risk patients as determined by pre-procedural CT scans, can actually reduce pneumothorax occurrence.

Blocking collateral ventilation

The majority of patients with heterogeneous emphysema has collateral ventilation and is therefore not suitable for endobronchial valve treatment. If we could close the collateral channels and afterwards perform an endobronchial valve treatment, the overall efficacy of bronchoscopic lung volume reduction would improve and a larger group of emphysema patients could be served. Autologous blood can be a potential substance to close off these collateral channels. The proposed mechanism is that the instilled autologous blood induces a mild inflammatory reaction, which combined with clotting itself, leads to scarring, fibrosis and the closing of the collateral channels. The use of autologous blood in the treatment of giant bullae in patients with emphysema has shown promising results, though admittedly the underlying pathology was different. Nevertheless, the treatment was safe and minimally invasive.[21] Furthermore, autologous blood is used in the treatment of a persistent air leak for example primary pneumothorax [22] and in some countries where there is no access to devices, lung volume reduction is conducted with autologous blood.[23] The advantage of the use of patient's own blood is that there are almost no device or experimental substance costs. A prospective, safety and feasibility study is needed to investigate if autologous blood, or another obLiterating agent, can be used to close the collateral channels.

Treatment for COPD patients with the bronchitis phenotype

Patients with the emphysema phenotype have parenchymal destruction and are therefore potential candidates for bronchoscopic lung volume reduction. Patients with the bronchitis phenotype, whether or not also with marked emphysema, have significant sputum production and sometimes frequent exacerbations with often better preserved lung tissue. Those patients are not eligible for endobronchial valve or coil treatment, due to the increase of infectious complications. We recently performed the first-in-human study investigating bronchoscopic radio-frequent ablation of the parasympathetic pulmonary nerves in patients. In this technique called targeted lung denervation, energy is delivered via a dual-cooled radiofrequency catheter (Holaira, Inc., Minneapolis, MN, USA) designed to target tissue heating at a certain depth thereby ablating nerves around the main bronchi while minimizing effects to the inner surface of the airway. The first results showed that the targeted lung denervation treatment was feasible, safe, and potentially clinically effective. The improvements in spirometry appear durable, dose dependent and potentially additive to inhaled anticholinergic.[24] Further investigation is needed to evaluate procedural safety and performance of the Holaira System. A randomized sham controlled trial would be ideal to investigate the treatment effects of targeted lung denervation. Currently, further product development in a feasibility trial to establish the optimal energy level are underway (ClinicalTrials.gov NCT02058459).

References

1. Herth FJ, Eberhardt R, Gompelmann D, et al. Radiological and clinical outcomes of using Chartis to plan endobronchial valve treatment. Eur Respir J 2013;41:302-8.

2. Davey C, Zoumot Z, Jordan S, et al. Bronchoscopic lung volume reduction with endobronchial valves for patients with heterogeneous emphysema and intact interlobar fissures (the BeLieVeR-HIFi study): a randomized controlled trial. Lancet 2015;386:1066-73.

3. Gompelmann D, Herth FJ, Slebos DJ, et al. Pneumothorax following endobronchial valve therapy and its impact on clinical outcomes in severe emphysema. Respiration 2014;87:485-91.

4. Valipour A, Slebos DJ, de Oliveira HG, et al. Expert statement: pneumothorax associated with endoscopic valve therapy for emphysema-potential mechanisms, treatment algorithm, and case examples. Respiration 2014;87:513-21.

5. Sciurba FC, Ernst A, Herth FJ, et al. A randomized study of endobronchial valves for advanced emphysema. N Engl J Med 2010;363:1233-44.

6. Herth FJ, Noppen M, Valipour A, et al. Efficacy predictors of lung volume reduction with Zephyr valves in a European cohort. Eur Respir J 2012;39:1334-42.

7. Herth FJ, Eberhardt R, Gompelmann D, et al. Radiological and clinical outcomes of using Chartis to plan endobronchial valve treatment. Eur Respir J 2013;41:302-8.

8. Venuta F, Anile M, Diso D, et al. Long-term follow-up after bronchoscopic lung volume reduction in patients with emphysema. Eur Respir J 2012;39:1084-9.

9. Hopkinson NS, Kemp SV, Toma TP, et al. Atelectasis and survival after bronchoscopic lung volume reduction for COPD. Eur Respir J 2011;37:1346-51.

10. Fishman A, Martinez F, Naunheim K, et al. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. N Engl J Med 2003;348:2059-73.

11. Shah PL, Slebos DJ, Cardoso PF, et al. Bronchoscopic lung-volume reduction with Exhale airway stents for emphysema (EASE trial): randomized, sham-controlled, multicentre trial. Lancet 2011;378:997-1005.

12. Slebos DJ, Hartman JE, Klooster K, et al. Bronchoscopic Coil Treatment for Patients with Severe Emphysema: A Meta-Analysis. Respiration 2015;90:136-45.

13. Stoller JK, Gildea TR, Ries AL, Meli YM, Karafa MT, National Emphysema Treatment Trial Research Group. Lung volume reduction surgery in patients with emphysema and alpha-1 antitrypsin deficiency. Ann Thorac Surg 2007;83:241-51.

14. Mahler DA, Faryniarz K, Tomlinson D, et al. Impact of dyspnea and physiologic function on general health status in patients with chronic obstructive pulmonary disease. Chest 1992;102:395-401.

15. Deslee G, Mal H, Dutau H, et al. Lung Volume Reduction Coil Treatment vs Usual Care in Patients With Severe Emphysema: The REVOLENS Randomized Clinical Trial. JAMA 2016;315:175-84.

16. Schuhmann M, Raffy P, Yin Y, et al. Computed tomography predictors of response to endobronchial valve lung reduction treatment. Comparison with Chartis. Am J Respir Crit Care Med 2015;191:767-74.

17. Klooster K, Ten Hacken NH, Hartman JE, Kerstjens HA, van Rikxoort EM, Slebos DJ. Endobronchial Valves for Emphysema without Interlobar Collateral Ventilation. N Engl J Med 2015;373:2325-35.

18. Fuehner T, Clajus C, Fuge J, et al. Lung Transplantation after Endoscopic Lung Volume Reduction. Respiration 2015;90:243-50.

19. Dejene S, Ahmed F, Jack K, Anthony A. Pneumothorax, music and balloons: A case series. Ann Thorac Med 2013;8:176-8.

20. Herzog D, Poellinger A, Doellinger F, et al. Modifying Post-Operative Medical Care after EBV Implant May Reduce Pneumothorax Incidence. PloS One 2015;10(5):e0128097.

21. Zoumot Z, Kemp SV, Caneja C, Singh S, Shah PL. Bronchoscopic intrabullous autologous blood instillation: a novel approach for the treatment of giant bullae. Ann Thorac Surg 2013;96:1488-91.

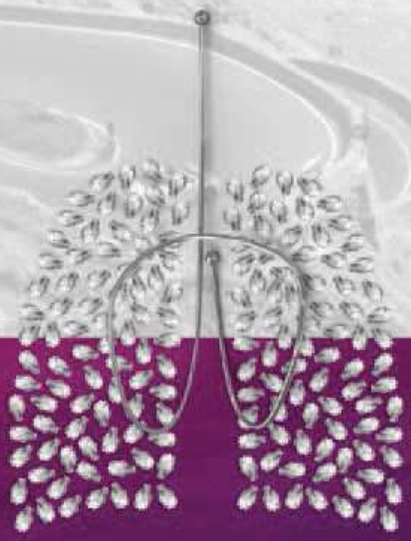
22. Manley K, Coonar A, Wells F, Scarci M. Blood patch for persistent air leak: a review of the current literature. Curr Opin Pulm Med 2012;18:333-8.

23. Mizumori Y, Mochiduki Y, Nakahara Y, et al. Effects of bronchoscopic lung volume reduction using transbronchial infusion of autologous blood and thrombin in patients with severe chronic obstructive pulmonary disease. J Thorac Dis 2015;7:413-21.

24. Slebos DJ, Klooster K, Koegelenberg CF, et al. Targeted lung denervation for moderate to severe COPD: a pilot study. Thorax 2015;70:411-9.

CHAPTER

14



Nederlandse samenvatting

Nederlandse samenvatting voor de niet medisch geschoolde lezer

In dit hoofdstuk volgt kort in het Nederlands een uitleg over COPD, hoe vaak de ziekte voorkomt en wat de huidige behandeling is. Vervolgens wordt er uitgelegd wat hyperinflatie is en er wordt uitleg gegeven over de nieuwe 'aanvullende' behandel opties voor patiënten met ernstig COPD die in dit proefschrift zijn onderzocht. Afsluitend is er een samenvatting van de belangrijkste bevindingen uit dit proefschrift.

COPD is de Engelse afkorting voor Chronic Obstructive Pulmonary Disease, ofwel chronische obstructieve longziekte. In Nederland wordt het aantal COPD patiënten geschat op 400.000 patiënten en is het een van de vijf meest voorkomende doodsoorzaken.[1] Het aantal patiënten met ernstig tot zeer ernstig COPD in Nederland wordt geschat op 50.000.[1] COPD is een ongeneeslijke ziekte.

COPD is een verzamelnaam voor chronische bronchitis en longemfyseem. Bij chronische bronchitis zijn de vertakkingen van de luchtpijp (de bronchiën) regelmatig of steeds ontstoken waardoor er meer slijm aangemaakt wordt in de luchtwegen. Door de ontsteking en slijmproductie zijn de luchtlijpjes vernauwd en wordt het ademen bemoeilijkt. Bij longemfyseem zijn de longblaasjes onherstelbaar beschadigd. De longblaasjes in de longen zijn uitgerekt en hierdoor verliezen de longen hun elasticiteit. Door de verminderde elasticiteit van de longblaasjes, is een er een constante belemmering van de uitademing. Patiënten met COPD kunnen last hebben van hoesten, slijm opgeven, en kortademigheid vooral tijdens inspanning zoals bijvoorbeeld traplopen, douchen en aankleden.

Bij patiënten met COPD is het totale longvolume toegenomen. Een groot deel van dit volume kan uitgeblazen worden, maar er blijft altijd een deel in de longen achter wat niet uitgeblazen kan worden, dit wordt ook wel het restvolume of residuale volume genoemd. Het volume wat maximaal uit geblazen kan worden en vervolgens weer zo diep mogelijk ingeademd kan worden wordt het verplaatsbaar volume of de vitale capaciteit genoemd. Bij gezonde mensen is het restvolume circa 2 Liter en het verplaatsbaar volume circa 4 Liter. Echter bij patiënten met COPD, is de uitademing erg belemmerd, waardoor het minder goed lukt om alle lucht uit te blazen. Hierdoor neemt het restvolume toe en het verplaatsbaar volume af. Bij patiënten met ernstig COPD is het restvolume vaak erg hoog, wel 4 Liter of nog hoger. Dat betekent dat er dan weinig verplaatsbaar volume overblijft. Dit wordt ook wel statische hyperinflatie genoemd. Doordat er weinig verplaatsbaar volume is, ervaart de patiënt kortademigheid. Tijdens inspanning is er bovendien nog minder tijd om volledig uit te ademen, hierdoor neemt het restvolume nog verder toe. Dit wordt ook wel dynamische hyperinflatie genoemd, hierdoor wordt de patiënt nog meer kortademig.

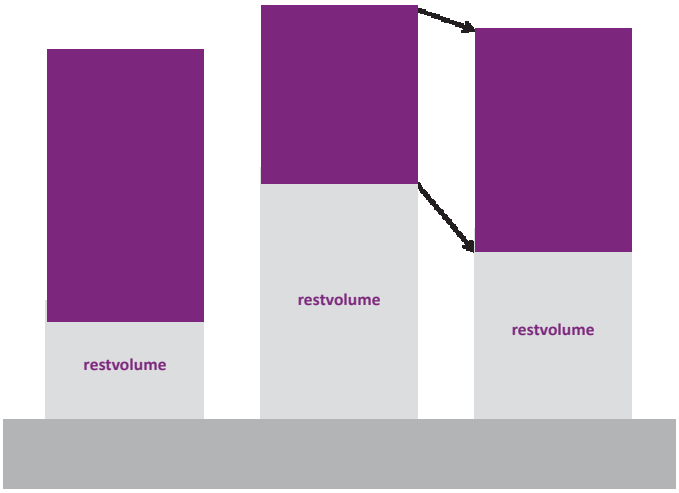
COPD verschilt van mens tot mens en daarom ook de behandeling. De verdere verslechtering kan geremd worden door te stoppen met roken en het voorkomen en goed behandelen van exacerbaties (ook wel longaanvallen genoemd).[2] Daarnaast is de behandeling vooral gericht op het verminderen van klachten. Maximale luchtwegverwijding met inhalatiemedicatie, voldoende bewegen en longrevalidatie spelen hierin een belangrijke rol. Alleen bij hoge uitzondering komen patiënten met een ver gevorderd stadium COPD in aanmerking voor

een longtransplantatie of longvolumereductie operatie. Bij longvolumereductie wordt operatief een stuk van de toppen van beide longen afgesneden zodat de resterende delen beter kunnen functioneren. Beide behandelingen zijn erg belastend voor de patiënt, omdat dit hele grote operaties zijn.

Voor patiënten met ernstig COPD is er daarom behoefte aan een niet-operatieve, minder belastende behandeling als aanvulling op de huidige behandeling. De afdeling Longziekten van het Universitair Medisch Centrum Groningen is in 2006 begonnen met het opzetten van een programma dat specifiek gericht is op het ontwikkelen van nieuwe, minimaal belastende behandelingen voor patiënten met ernstig COPD. Deze behandelingen worden bronchoscopische longvolumereductie genoemd. De bronchoscopische longvolumereductie mogelijkheden die in dit proefschrift beschreven worden, zijn een behandeling met eenrichtingsventielen en een behandeling met coils.

Tijdens een bronchoscopie wordt een bronchoscoop, dat is een buigzame slang met aan het uiteinde een lens, via de neus of mond in de luchtpijp ingebracht. Hierdoor kunnen de luchtwegen van de binnenkant bekeken worden. Via de bronchoscoop is het mogelijk om een katheter (dun slangetje) op te voeren waarmee de eenrichtingsventielen of coils ingebracht kunnen worden. De behandeling gebeurt terwijl de patiënt in slaap is gebracht door de anesthesioloog.

Bronchoscopische longvolumereductie met eenrichtingsventielen is een bronchoscopische procedure waarbij de ingang van een longkwab met een aantal eenrichtingsventielen afgesloten wordt. De kleine ventielen zijn gemaakt van metaal met een laagje siliconen er omheen. De eenrichtingsventielen zijn zo gemaakt dat ze bij inademing dicht blijven en bij uitademing open gaan en lucht naar buiten laten gaan. Hierdoor zal de longkwab die behandeld is volledig ontluchten en samenvallen, wat voor de longvolumereductie zorgt. De longkwab kan alleen kleiner worden als de ingang van de longkwab volledig afgesloten wordt met eenrichtingsventielen én als er geen luchtstroom in de behandelde kwab kan komen via de aanliggende kwab (dit heet ook wel “collaterale ventilatie”). Door het plaatsen van eenrichtingsventielen, worden de meest aangetaste longdelen afgesloten, hierdoor zal het restvolume kleiner worden waardoor het verplaatsbaar volume weer groter wordt.



Bronchoscopische longvolumereductie met coils is een procedure waarbij er coils in de luchtwegen van beide longen geplaatst worden. Een coil is een elastische draad gemaakt van geheugenmetaal (nitinol). De coil krult na inbrengen in de aangedane luchtwegen als een varkensstaart of veer op, waardoor het aangetaste weefsel bijeen getrokken wordt. Hierdoor worden de overblijvende luchtwegen weer wijder waardoor lucht gemakkelijker uitgeademd kan worden. Zo wordt het restvolume weer kleiner en het verplaatsbaar volume groter. Mogelijk wordt ook de longelasticiteit verbeterd waardoor het longweefsel beter kan functioneren.

Samenvattend

Voor patiënten met zeer ernstig COPD zijn de huidige behandelopties als stoppen met roken, optimale medicatie, goede voeding, longrevalidatie, zuurstof en beademing onvoldoende effectief. Voor slechts een hele kleine groep van deze patiënten is longvolumereductie operatie of longtransplantatie mogelijk. Deze behandelingen zijn erg belastend, schaars en duur. Daarom zijn minder belastende longvolumereductie behandelingen ontwikkeld. In dit proefschrift onderzochten we twee nieuwe bronchoscopische behandelingen bij patiënten met ernstig emfyseem; longvolumereductie behandeling met eenrichtingsventielenen met coils.

Resultaten

In **hoofdstuk 2** worden foto's gepresenteerd van de binnenkant van een long. Op deze foto's is een indrukwekkend beeld te zien van de weefselafbraak in de long van een patiënt met ernstig emfyseem. De longblaasjes en bloedvaten zijn beschadigd en daarom is de functie van de longen zeer beperkt. Bovendien is het longweefsel beschadigd waardoor er verminderde elasticiteit is van de longen. Door de verminderde elasticiteit van de longblaasjes zullen tijdens het uitademen de luchtwegen dichtvallen waardoor de ingeademde lucht moeilijk eruit kan.

In **hoofdstuk 3** wordt een overzicht (in het Nederlands) gepresenteerd over de huidige status van bronchoscopische behandelingen bij patiënten met ernstig COPD. Het overzicht beschrijft de al gepubliceerde gegevens van zowel de coil behandeling als de behandeling met eenrichtingsventielen. Het is afhankelijk van het soort emfyseem of een patiënt kan worden behandeld met een van deze technieken, en zo ja met eenrichtingsventielen of met coils. In hoofdstuk 5 is laten we belangrijke aanvullende resultaten zien van de behandeling met eenrichtingsventielen. Er wordt ook een praktijksituatie gepresenteerd van een patiënt die een behandeling met eenrichtingsventielen heeft ondergaan.

In **hoofdstuk 4** worden de resultaten getoond van een onderzoek naar de rol van dynamische hyperinflatie bij patiënten met ernstig COPD. In deze studie werd gemeten in welke mate het inademingsvolume afneemt tijdens een nagebootste inspanning. Dan is dus het verplaatsbaar volume afgenomen en het restvolume toegenomen, ofwel er is hyperinflatie. Bij patiënten met ernstig COPD hebben wij onderzocht of het mogelijk is om een test uit te voeren die de problemen bij inspanning voor mensen met ernstig COPD nabootst. Daarbij wordt de patiënt gevraagd gedurende een minuut met een vaste hoge ademfrequentie te ademen en nadien vervolgens nog gevraagd een maximale inademing te doen. We bepaalden de relatie tussen de zo gemeten dynamische hyperinflatie en de loopafstand behaald in de 6 minuten wandeltest. De test werd goed verdragen door de patiënten en we zagen dat we met deze test het inademingsvolume inderdaad afnam. In tegenstelling tot wat we verwacht hadden, bleek echter niet de dynamische hyperinflatie, maar de statisch hyperinflatie de belangrijkste de beste voorspeller voor inspanningscapaciteit bij patiënten met zeer ernstig COPD.

In **hoofdstuk 5** worden de resultaten van de STELVIO studie gepresenteerd. In deze studie hebben we het effect van de behandeling met eenrichtingsventielen onderzocht bij patiënten met ernstig emfyseem. Het effect van de behandeling met eenrichtingsventielen was al eerdere onderzocht. Uit voorgaande studies is gebleken dat het belangrijk is dat er geen 'lekkage' is tussen de longkwab waarin ventielen worden geplaatst en de aanliggende longkwab. Lekkage tussen twee longkwabben wordt ook wel collaterale ventilatie genoemd. Tijdens een bronchoscopie konden we met behulp van een katheter en een ballonnetje meten of er wel of geen collaterale ventilatie is. Alleen als er geen collaterale ventilatie was kwam de patiënt in aanmerking voor de behandeling met eenrichtingsventielen. Door middel van een loting kreeg de ene helft van de patiënten direct de eenrichtingsventielen geplaatst en de andere helft kreeg de ventielen pas na 6 maanden. De verwachting was dat

patiënten 6 maanden na het plaatsen van eenrichtingsventielen een betere longfunctie, inspanningsvermogen en kwaliteit van leven zouden hebben in vergelijking met de mensen die geen behandeling kregen met eenrichtingsventielen. In deze studie konden wij inderdaad aantonen dat de behandeling met eenrichtingsventielen klinisch relevante verbeteringen gaf in alle drie genoemde uitkomsten in de goed geselecteerde groep van patiënten met ernstig emfyseem zonder aanwezigheid van collaterale ventilatie. Er waren ook bijwerkingen van de behandeling. De meest voorkomende bijwerking van de behandeling met eenrichtingsventielen was een klaplong. Bij de meeste patiënten was hiervoor een behandeling met een thoraxdrain, een slangetje tussen de ribben door om lucht af te zuigen, afdoende. Soms genas de klaplong echter niet gemakkelijk, waarbij het nodig was één van de geplaatste ventielen tijdelijk te verwijderen. In sommige gevallen, zoals bij een terugkerende klaplong of bij het losraken van eenrichtingsventielen ten gevolge van bijvoorbeeld ontstekingsweefsel, was het ook een aantal keer noodzakelijk om de ventielen definitief te verwijderen.

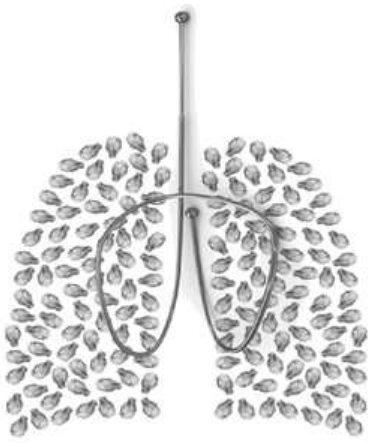
In het onderzoek beschreven in **hoofdstuk 6** onderzochten we de dagelijkse lichaamsbeweging voor en na de behandeling met eenrichtingsventielen. De hoop is namelijk dat mensen naar behandeling zich niet alleen beter kunnen inspannen maar dat ook echt doen. Met behulp van een accelerometer (een stappenteller) werden gedurende een week de bewegingen zoals liggen, zitten, staan en lopen geregistreerd. We vonden dat de dagelijkse lichaamsbeweging toenam 6 maanden na een longvolumereductie behandeling met eenrichtingsventielen, dit zonder verdere begeleiding of aanmoediging van de patiënt.

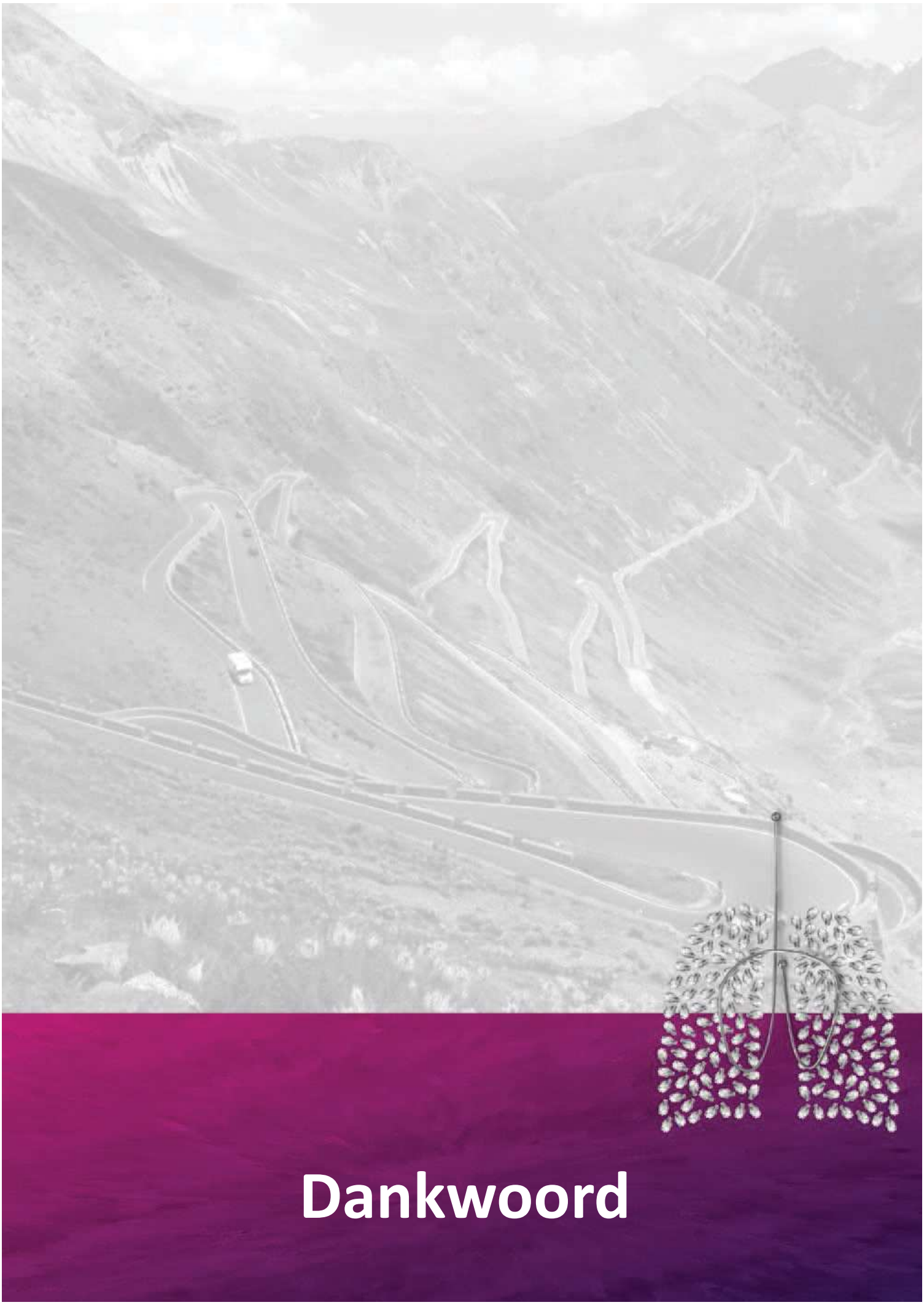
In de **hoofdstukken 7, 8 en 10** worden de resultaten van studies gepresenteerd waarin we de veiligheid, uitvoerbaarheid en de effectiviteit van de behandeling met longvolumereductie coils hebben onderzocht. We toonden aan dat plaatsing van de coils veilig uitgevoerd kan worden, en ook dat er klinisch relevante verbeteringen waren in de longfunctie, het inspanningsvermogen en de kwaliteit van leven. De belangrijkste bijwerkingen van de coil-behandeling zijn het optreden van COPD exacerbaties en infectieuze complicaties in de eerste paar maanden na de behandeling. In **hoofdstuk 9** hebben we de veiligheid en werkzaamheid van de longvolumereductie coil behandeling op lange termijn onderzocht. We zagen geen onverwachte bijwerkingen 3 jaar na plaatsing van de coils, maar wel de bijwerkingen die we ook op korte termijn al zagen. Het klinische effect van de behandeling neemt geleidelijk af en is 3 jaar na de behandeling vrijwel op het uitgangsniveau. De beschreven onderzoeken zijn aanleiding geweest om nieuwe studies op te starten waarbij er een controle groep zal zijn. De ene groep zal wel een behandeling met coils krijgen (behandel groep) en de andere groep (controle groep) pas na 1 jaar. Vervolgens wordt dan de effectiviteit van de behandeling met coils vergeleken met mensen die geen behandeling hebben gekregen met coils. Deze studies moeten de effectiviteit van de behandeling met coils meer onderbouwen en meer inzicht geven in welke patiënten geschikt zijn voor de behandeling. In **hoofdstuk 11** wordt een overzicht van de ontwikkeling van de coil behandeling gegeven.

Afsluitend worden in **hoofdstuk 12** de resultaten samengevat, in **hoofdstuk 13** de resultaten bediscussieerd en worden een aantal ideeën voor verder onderzoek gepresenteerd. We hopen dat met deze mooie resultaten de behandeling met eenrichtingsventielen in de standaard, verzekerde zorg voor COPD komt. Daarnaast hopen we dat er in de nieuwe studies de effectiviteit van de coil behandeling aangetoond wordt en met name dat we meer inzicht krijgen welke patiënten er geschikt zijn voor de behandeling met coils, zodat ook deze behandeling in de standaard, verzekerde zorg voor COPD kan komen.

Referenties

1. COPD. In: Longziekten, feiten en cijfers 2013. Hfdst 2. Amersfoort: Long Alliantie Nederland; 2013. p. 34-47.
2. Vestbo J, Hurd SS, Agustí AG, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2013;187:347-65.





Dankwoord

Dankwoord

De afgelopen 3 jaar heb ik naast mijn werk als studie-coördinator en de begeleiding van patiënten met erg veel plezier aan mijn proefschrift gewerkt. Het proefschrift is dan nu wel af, maar wij gaan gewoon verder met het uitvoeren en ontwikkelen van nieuwe bronchoscopische behandelingen voor patiënten met COPD.

Vele patiënten zijn met hun familieleden vanuit heel Nederland zijn naar ons toegekomen met de hoop op een “beetje meer lucht”. De behandelingen die wij uitvoeren waren nog zeer experimenteel, ook wij wisten niet of de patiënt daadwerkelijk “meer lucht” zou krijgen, maar toch hebben de patiënten vertrouwen is ons gehad en deelgenomen aan onze onderzoeken. Ondanks hun benauwdheid en beperkingen was iedereen bereid om telkens maar weer een longfunctie test te blazen, gedurende zes minuten rondom de pionnen in de enorm lange gang heen en weer te lopen en telkens maar weer de vragenlijsten in te vullen. Daarom wil ik als eerste alle patiënten en hun familieleden die hebben deelgenomen aan de onderzoeken beschreven in dit proefschrift hartelijk danken voor het getoonde vertrouwen en hun geweldige medewerking.

Sinds 2006 zijn we in het UMCG begonnen met het bronchoscopisch interventiecentrum, de eerste patiënten kwamen voornamelijk uit de regio, echter doordat patiënten hun ervaringen deelden op ‘social media’ kwam er al snel een toestroom van verwijzingen uit het hele land. Patiënten legden de vraag voor aan hun longarts om zo een verwijzing naar Groningen te krijgen. Voor de longartsen was dit niet altijd eenvoudig, immers de behandelingen waren nog heel experimenteel en er was nog niet veel bekend over de effecten en de bijwerkingen. Als arts wil je natuurlijk het beste voor je patiënt en de vraag is of je de patiënt er wel mee helpt met één van die nieuwe ‘trucjes’. Het vertrouwen in de nieuwe behandelingen groeide, en in de loop der jaren zijn de verwijzingen enorm toegenomen: waar we in het eerste jaar circa 30 verwijzingen kregen, zitten we nu op meer dan 300 verwijzingen per jaar. Daarom wil ik alle verwijzende longartsen ook hartelijk danken voor het vertrouwen en de prettige samenwerking.

Vervolgens wil ik iedereen bedanken, die op welke wijze dan ook, mij heeft geholpen. Bij het uitvoeren van onderzoek heb je te maken met vele afdelingen, het is dan ook geweldig dat die samenwerking altijd erg goed liep. Nooit geen wachttijden voor het plannen van veel onderzoeken, met altijd enorme flexibiliteit. Een aantal afdelingen en mensen wil ik graag in het bijzonder bedanken.

De longfunctieafdeling wil ik bedanken voor de ontzettend leuke tijd die ik heb gehad toen ik zelf daar werkte en voor het inplannen en uitvoeren van de vele longfunctietesten. Naast alle longfunctie assistenten wil ik in het bijzonder Martijn Farenhorst, Marga Star, Yvonne Valkema, Margrietha Swierenga, Jan Bouwman, Maria Heuving bedanken voor de zeer prettige begeleiding van ‘onze’ patiënten. Aly van der Laan, José Hovinga, Wies Heins en Jenny Stevens, hartelijk dank voor het inplannen van de onderzoeken.

De afdeling Radiologie wil ik bedanken voor de plezierige samenwerking en flexibiliteit. De medewerkers die alle foto's en CT scans inplannen en altijd bereid zijn om een plekje te vinden voor onze patiënten, de vriendelijke baliemedewerkers die onze patiënten verwelkomen en alle radiodiagnostische laboranten voor het uitvoeren van de onderzoeken en flexibele inzet als er tussendoor 'even' en patiënt gescand moet worden. De systeemspecialisten Wim Tukker en Ronald Dob die er voor zorgen dat de correcte CT protocollen ingesteld zijn en dat de kwaliteit van de scans gewaarborgd zijn. De algemene ondersteuning van de radiologie; Jorrit de Wiljes , André Broekema, Florian van de Werf en Remko Roosjen; altijd gezellig om even bij jullie langs te lopen en dank voor jullie goede en snelle service van het afleveren van de beelden. De betrokken radiologen; Rienhart Wolf, Gonda de Jonge, Rozemarijn Vliegenhart en Tineke Willems. De research afdeling en de research coördinator Stella Noach, bedankt voor het behandelen van de onderzoeksprotocollen.

Alle medewerkers van de verpleegafdeling D3VA. Onze patiënten zijn bij jullie in goed handen. Hartelijk dank voor het liefdevol opvangen, verzorgen en verplegen van onze patiënten. Jullie enorme betrokkenheid, enthousiasme en interesse in het bronchoscopisch interventie programma wordt enorm gewaardeerd.

De opname coördinatoren, Anna-Mieke van der Zee en Jacoba Mollema, bedankt voor het inplannen van de opnames, erg prettig dat in overleg eigenlijk altijd alles mogelijk is.

De secretaresses van het endoscopiecentrum wil ik bedanken voor het inplannen van de bronchoscopiën. Daarnaast de endoscopie verpleegkundigen Elma Ringenier, Karla Knol, Marije Ottens en Wiesje Giezen, dank voor jullie hulp en goede zorgen tijdens de bronchoscopiën. In het bijzonder wil ik Alie Smidt bedanken, jij was de 'rechter hand' tijdens de interventies en was bij alle nieuwe ontwikkelingen betrokken. Tijdens de bronchoscopiën had jij de regie in handen en zorgde jij ervoor dat alles keurig verliep. Tijdens speciale gelegenheden werden wij getrakteerd op een bonbon uit een doosje die veilig opgeborgen stond in een kast met een deur met sleuteltje!

Alle anesthesiologen en anesthesiologie assistenten, dank voor jullie lieve zorgen. Het is voor onze patiënten erg fijn dat jullie de anesthesie op het endoscopiecentrum verrichten. In het bijzonder wil ik Ina Franz bedanken, vanaf het 'begin' ben jij enorm betrokken bij ons programma en ben jij bij vele procedures aanwezig. Daarnaast ook Gritta Krenz en Boukes Eindhoven, bedankt voor jullie enthousiasme en betrokkenheid en natuurlijk ook de procedures waarbij wij de 'jet ventilatie' nodig hadden. Ook alle medewerkers van de POPA wil ik bedanken voor het inplannen en voor het verrichten van de preoperatieve screeningen.

De medewerkers van de polikliniek longziekten; Tineke Wendel, Maaike Hoekstra, Esther Alkema, Liane Abuys, Maaike Tamminga, Marieke Norden en Marianne Nijdam. Dank voor het vriendelijk ontvangen van onze patiënten, het versturen van de brieven en alle andere hulp.

Alle echocardiografie laboranten van de afdeling cardio research en Joost van Melle, Yoran Hummel en Karin de Jonge, hartelijk dank voor het uitvoeren van de echo's, beoordelen, inplannen en de altijd snelle verslaglegging hiervan.

Alle stafleden en arts-assistenten van de afdeling longziekten, bedankt voor al jullie interesse, steun, vertrouwen en de 24/7 hulp, onmisbaar voor het bestaan van ons programma en het uitvoeren van de studies. Ook met het team van de afdeling longrevalidatie in Beatrixoord, het team van de long transplantatie en de thoraxchirurgie, zijn er hele snelle 'korte' lijnen ontstaan en hebben hiermee het beste voor de patiënt kunnen bereiken.

Dirkje; ik wil je enorm bedanken voor jouw vertrouwen in mij, je enthousiasme en belangstelling voor de onderzoeken. Vanaf het begin dat ik op de longfunctieafdeling kwam werken ging mijn interesse al uit naar het doen van onderzoek. Als longfunctie-assistent heb ik altijd met veel enthousiasme aan diverse studies meegewerkt en heb ik vele verdedigingen meegemaakt. Mijn wens was destijds al om ook ooit een keer mijn eigen verdediging te mogen houden in het Academiegebouw. Ik kan mij nog goed herinneren dat jij op een dag aan mij vroeg of ik het zag zitten om een promotietraject in te gaan. Uiteraard voelde ik mij erg gevleid, echter op dat moment was ik net moeder geworden en vond het ook super leuk om heerlijk moeder te zijn en ik wilde dit moederschap niet "delen" met een promotie traject. Toch heb ik dit altijd in mijn achterhoofd gehouden en jouw vertrouwen in mij heeft mij ook enorm geholpen toen ik besloten heb om uiteindelijk, jaren later toch dit traject in te gaan.

Judith Vonk van de afdeling epidemiologie wat fijn dat ik naar aanleiding van een review vraag van de NEJM dezelfde dag nog bij jou terecht kon om uitleg te krijgen over de 'intention to treat analyses'.

Laurens Hoogeweg en Eva van Rikxoort, hartelijk dank voor het analyseren van de CT scans.

De secretaresses van de longafdeling wil ik hartelijk danken voor alle hulp en ondersteuning. Daarnaast is het altijd leuk om bij jullie binnen te lopen en gezellig te kletsen. Trudy Carbo, dank voor al jouw hulp, bestelling van 'devices', regelen van afspraken en alle andere ondersteuning. Bedankt voor het doorverbinden van dat ene telefoontje, mede doordat jij een bedrijf doorverbond naar Dirk-Jan is het bronchoscopisch interventie programma van start gegaan. Heleen Kruger, hartelijk dank voor het 'regelen' van de afspraken met Huib, de telefoontjes van patiënten doorverbinden en alle andere hulp.

Medische Etische Toetsings commissie van het UMCG; Jan Davids, John de Vroedt, Joke Ummels, Barbara Orkwiszewska en alle overige medewerkers. In de afgelopen jaren hebben wij vele nieuwe onderzoeken ingediend, er is veel vergaderd en er zijn vele stukken heen en weer gegaan. De samenwerking was altijd erg prettig.

Astrid Schulenklopper en Ruth Hiltermann, nog voordat ik mijn promotie traject in ben gegaan heb ik enorme ondersteuning gehad van jullie. Hartelijk dank voor al jullie inzet, voor het uitvoeren van de wandeltesten, het inplannen van patiënten, allerlei andere werkzaamheden en jullie fijne samenwerking.

Mijn lieve collega's van het bronchoscopisch interventie centrum wil ik bedanken voor de gezellige samenwerking. Nadat ik de eerste jaren alleen was en 1 bureau met kast had, zijn we inmiddels enorm uitgebreid. We hebben nu een eigen kamer, met 4 bureaus, 3 kasten en een 'walk-in-closet' (de droom van iedere vrouw) met nog eens 7 kasten voor onze devices en binders. Beste Gea, Sonja en Jorine het is erg fijn om met jullie samen te werken en ik hoop nog lange tijd zo door te gaan.

Mijn mede onderzoekers van de afdeling longziekten; bedankt voor de gezellige sfeer, jullie betrokkenheid en de leuke dingen na werktijd (schaatsen, bowlen, poolen, eten etc.).

Mijn promotor:
Prof. dr. Huib Kerstjens; Beste Huib, hartelijk dank dat je mij de kans hebt gegeven om het promotietraject in te gaan. Dank voor het meedenken, stellen van kritische vragen en het beter maken van de artikelen. Ik heb je snelle en concrete commentaren op de manuscripten erg gewaardeerd.

Mijn co-promotor:
Dr. Dirk-Jan Slebos, Beste Dirk-Jan; onze samenwerking is circa 15 jaar geleden begonnen nadat ik destijds data verzamelde en ingevoerd heb voor jouw promotie traject. Na je promotie, nadat je terug kwam uit Pittsburgh ging jij je focussen op de bronchoscopische interventies. In 2006 werd jij 'principal investigator' van de EASE trial en ik deed de longfunctietesten bij de patiënten die deelnamen aan deze studie. Halverwege de studie werd ik tevens studie-coördinator. Omdat we deze studie succesvol uitgevoerd hebben, met een hoog aantal gerandomiseerde patiënten werd jij, tijdens het ERS congres in Berlijn in 2008, door vele 'device companies' benaderd om experimentele bronchoscopische interventies uit te voeren, allen in studieverband. In 2010 heb jij een ZonMw subsidie in de wacht gesleept en je hebt hierdoor je eigen 'investigator initiated ' onderzoek kunnen opzetten "De STELVIO trial". Gedurende de trial ontstond de behoefte om een promovendus aan te stellen en gelukkig voor mij kon ik deze vacature opvullen. Ik wilde graag naast de patiëntenzorg waar altijd al mijn hart lag het 'complete plaatje' mét onderzoek, en daarbij hoort ook promoveren. Samen vormen we een goed team en zijn we inmiddels uitgegroeid tot een van de toonaangevende centra wereldwijd op dit gebied. Door jouw enorme inzet, betrokkenheid en deskundigheid ben jij inmiddels een expert geworden op het gebied van de bronchoscopische longvolumereductie.

Mijn co-promotor:
Dr. Nick ten Hacken: Beste Nick; toen in 2013 er een vacature was voor "arts promovendus" begon ik 'm een beetje te knijpen. Want al een aantal jaren hield ik mij bezig met het opzetten en uitvoeren van onderzoeken op het gebied van bronchoscopische longvolumereductie, was ik bij iedere interventie, kende ik alle patiënten en had ik inmiddels al veel onderzoekdata

verzameld. Eigenlijk deed ik ook al een beetje het werk van een promovendus, behalve het analyseren en schrijven. Maar ik dacht; “dat kan ik ook leren”, en toch twijfelde ik daarover. Jij bent diegene geweest die mij overtuigd heeft om wel de uitdaging aan te gaan. We liepen de trap af van de 3de verdieping en jij gaf mij een schouderklop en zei; ‘maar Karin dat kan jij toch ook’. Dit was net het laatste duwtje wat ik nodig had. Hartelijk dank hiervoor! Bedankt voor alle leuke gesprekken, jouw prettige begeleiding en je input tijdens het promotietraject.

Mijn co-promotor:
Dr. Jorine Hartman; Beste Jorine, nadat jij nog maar net zelf gepromoveerd was kwam jij in 2013 bij ons team werken. Erg fijn dat we coördineerde en uitvoerende werkzaamheden samen konden doen, zodat ik wat meer tijd kreeg voor de “wetenschap”. Super handig dat ik o.a. voor statistiekvragen en de trucjes van Adobe InDesign bij jou terecht kan. Dank voor alle input.

De leescommissie, bestaande uit Prof. dr. Dirkje Postma, Prof. dr. J. Annema en Prof. dr. M. Mariani, wil ik hartelijk danken voor de bereidheid tot het lezen en beoordelen van dit proefschrift.

I would like to thank all the co-authors for their contribution to the manuscripts in this thesis; Frank C. Sciurba, Pittsburgh, USA; Michiel Erasmus; Ina Franz; Huib A.M. Kerstjens, Dirk-Jan Slebos; Nick H.T. ten Hacken; Jorine E. Hartman; Kiki Gortzak Groningen, The Netherlands; Eva van Rikxoort, Nijmegen, The Netherlands; Armin Ernst, Boston, USA; Romain Kessler, Strasbourg, France; Gaëtan Deslee, Reims, France; Charles-Hugo Marquette, Nice, France; Martin Hetzel, Stuttgart, Germany; Franz Stanzel, Hemer, Germany; Christian Witt, Berlin, Germany; Stefan Blaas, Donaustauf, Germany; Wolfgang Gesierich, Gauting, Germany; Juergen Hetzel, Tübingen, Germany and Felix Herth, Heidelberg, Germany.

The studies in this thesis were not possible without the financial support from the Organization for Health Research and Development ZonMw, the University Medical Center Groningen and the device companies; Pulmonx Corporation and PneumRx, a BTG International group company.

Thank you for the financial support of printing this thesis; Pulmonx Corporation; PneumRx, a BTG International group company; Holaira Inc.; CSA medical Inc.; Forbion Capital Partners; Endeavour Vision; Chiesi Pharmaceuticals B.V.; Boehringer Ingelheim B.V.; Olympus B.V.; the Graduate School of Medical Sciences of the University Medical Center Groningen and the University of Groningen. I really appreciate your contribution.

Thanks to everyone who contributed to the monitoring of our studies. Together we were a good team with the same goal to collect solid data for the studies.

I would like to thank all the people who we work with from Pulmonx, PneumRx, Holaira, and CSA medical. I so nice to do research with you all.

Dr. Pallav Shah, dear Pallav; thank you for being a friend and for together exploring the bronchoscopic intervention field.

Prof. dr. Masamichi Mineshita, dear Masa; thank you for your enthusiasm and interest in the bronchoscopic intervention field. Nice to have a 'Groningen hometown' friend who lives in Japan.

Dr. Frank Sciurba, dear Frank; thank you for the interesting dicussions about dynamic hyperinflation and pulmonary function tests. It was also very nice to do together the live bronchoscopy sessions during the ERS conference in Amsterdam.

Graag wil ik iedereen bedanken die hier nog niet genoemd zijn, maar mij in al die jaren hebben bijgestaan. Lieve familie, schoonfamilie, vrienden en buren. Fijn dat ik altijd bij jullie terecht kan en dat jullie er altijd voor mij zijn.

Lieve papa en mama, dank voor jullie liefde en betrokkenheid. Bedankt voor hetgeen jullie mij meegeven hebben.

En er is natuurlijk veel meer in het leven dan promoveren.

'Het leven is als een rozenblad, van ontluiken tot ontvouwen.
Het leven is als een regenbad vol druppels van vertrouwen.
Het leven is geen stippellijn, waarlangs de wensen gaan.
Het leven is een mooi refrein, dat altijd door blijft gaan'

Marijke de Haan

Helaas Marijke heb jij de afronding van mijn proefschrift niet meer mee kunnen maken, maar ik wil je toch heel erg bedanken voor al jouw enthousiasme, vertrouwen en liefde die je mij gegeven hebt. In gedachten ben je bij ons. Bert, jouw betrokkenheid en gezelligheid zijn enorm waardevol.

Mijn paranimfen, mijn lieve dochters Marinda en Kalena. Wat ben ik super trots op jullie en wat vind ik het ontzettend leuk dat jullie mij ook op deze dag bijstaan. Lieve Jarwin, wat word ik blij van jouw vrolijkheid en enthousiasme, je bent een heerlijk mannetje.

Lieve Stijn en Olivier, al bijna 7 jaar mijn 'bonus' kinderen, wat is het leuk om samen één grote familie te zijn.

Mijn grote liefde. Lieve Dirk-Jan, wat is het fijn om iedere dag blij naast elkaar wakker te worden, samen naar ons werk te gaan en als we vrij zijn heerlijk samen te fietsen door Groningen, Drenthe of ergens in de bergen en andere leuke dingen te doen, maar vooral ook te genieten van 'onze' kinderen. Jij geeft mij zoveel vertrouwen in alles wat ik doe, je haalt het beste in mij naar boven.

"Omdat jij in mij geloofde en zei dat ik het kon
En omdat jij zei dat ik het beste was wat jou is overkomen
Heb jij mijn grens verlegd voorbij mijn horizon"

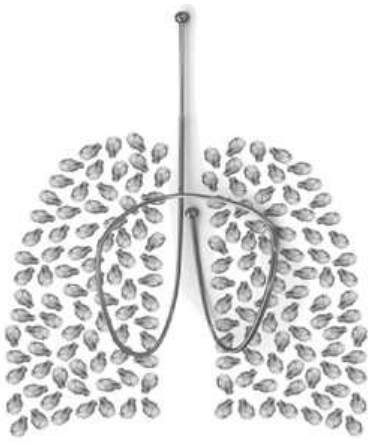
Paul van Vliet

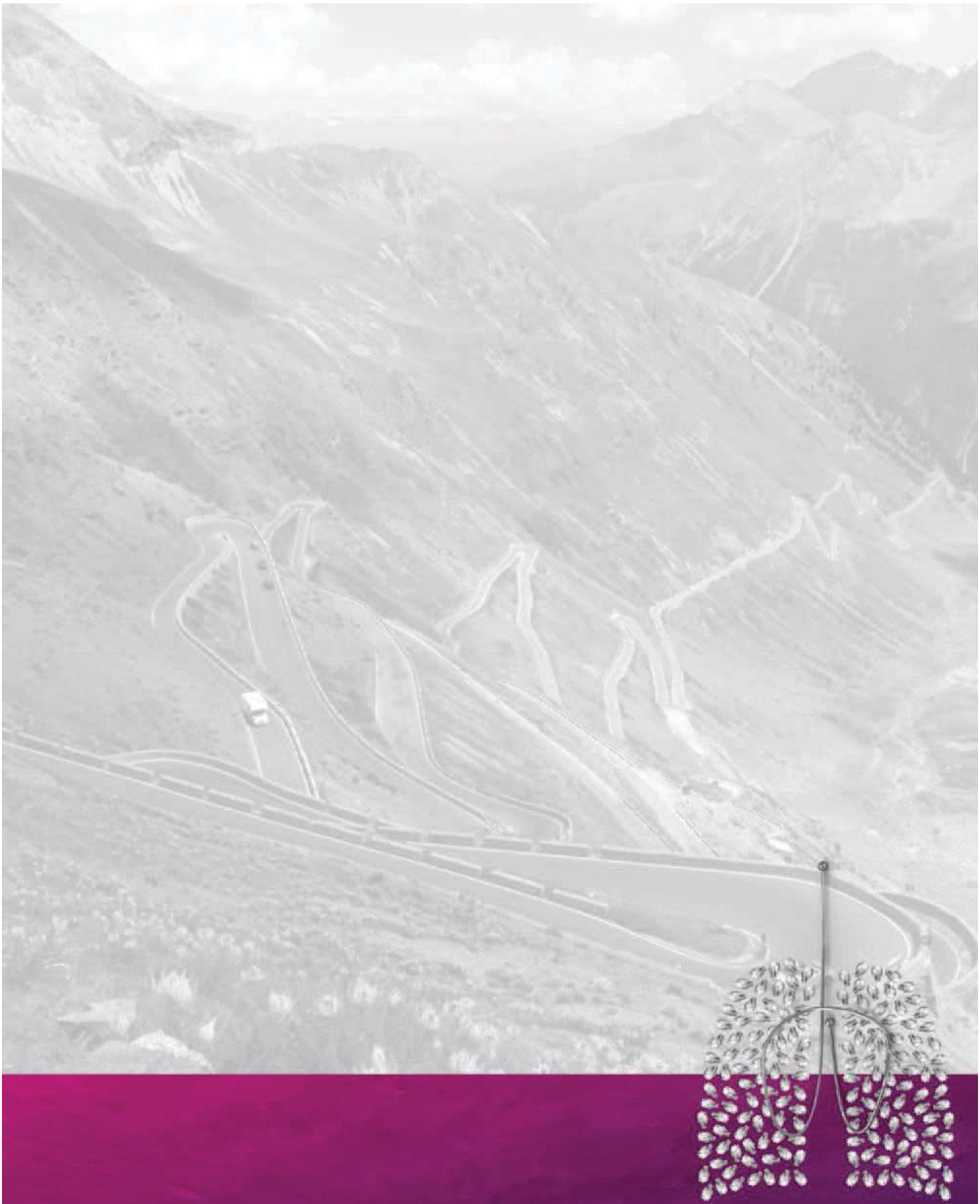
"When you reach the top, that's when the climb begins '!

Michael Caine

Nogmaals aan iedereen: **Mijn dank is groot!**
En we gaan gewoon weer verder …

Karin





List of publications and curriculum vitae

List of publications

1. **Endobronchial valves for emphysema without interlobar collateral ventilation (The Stelvio trial)**
   Klooster K, ten Hacken NHT, Hartman JE, Kerstjens HAM, van Rikxoort EM, Slebos DJ
   New England Journal of Medicine 2015;373:2325-35.
   Denver, USA 2015; On behalf of the Assembly on Clinical Problems of the American Thoracic Society, the abstract"Endobronchial valves for emphysema without interlobar collateral ventilation" received a Dr. Sreedhar Nair Memorial Award given for top abstracts from the National Emphysema Foundation.
2. **Determining the role of dynamic hyperinflation in patients with severe COPD**
   Klooster K, ten Hacken NHT, Hartman JE, Kerstjens HAM, Sciurba F, Slebos DJ
   Respiration 2015;90;306-13.
3. **Bronchoscopische interventies voor patiënten met ernstig COPD**
   Klooster K, ten Hacken NHT, Hartman JE, Kerstjens HAM, Slebos DJ
   Nederlands Tijdschrift voor Geneeskunde 2015;159:A8497.
4. **Long-term follow-up after bronchoscopic lung volume reduction treatment with coils in patients with severe emphysema**
   Hartman JE, **Klooster K**, Gortzak K, Ten Hacken NHT, Slebos DJ
   Respirology 2015;20:319-26.
5. **Lung volume reduction coil treatment in chronic obstructive pulmonary disease patients with homogeneous emphysema: a prospective feasibility trial**
   Klooster K, Ten Hacken NHT, Franz I, Kerstjens HAM, van Rikxoort EM, Slebos DJ
   Respiration 2014;88:116-25.
6. **The lung volume reduction coil for the treatment of emphysema: a new therapy in development**
   Klooster K, ten Hacken NHT, Slebos DJ
   Expert Review of Medical Devices 2014;11:481-9.
7. **Lung volume reduction coil treatment for patients with severe emphysema: a European multicentre trial**
   Deslee G, **Klooster K**, Hetzel M, Stanzel F, Kessler R, Marquette CH, Witt C, Blaas S, Gesierich W, Herth FJ, Hetzel J, van Rikxoort EM, Slebos DJ
   Thorax 2014;69:980-6.
8. **Emphysema!**
   Slebos DJ, **Klooster K**, Erasmus M.
   American Journal of Respiratory and Critical Care Medicine 2012;186:197.
9. **Bronchoscopic lung volume reduction coil treatment of patients with severe heterogeneous emphysema**
   Slebos DJ, **Klooster K**, Ernst A, Herth FJ, Kerstjens HAM.
   Chest 2012;142:574-82.
10. **Improvement of physical activity after endobronchial valve treatment in severe emphysema patients**
    Hartman JE, **Klooster K**, Slebos DJ, ten Hacken NHT
    Submitted.

11. **"Another STEP forward in emphysema treatment"**
Slebos DJ. **Klooster K**
Lancet respiratory 2016; Electronic publication February 15th

12. **Targeted lung denervation for moderate to severe COPD: a pilot study**
Slebos DJ, **Klooster K**, Koegelenberg CFN, Theron J, Styen D, Valipour A, Mayse M, Bolliger CT
Thorax 2015;70:411-9.

13. **Treatment of emphysema using bronchoscopic lung volume reduction coil technology: an update on efficacy and safety**
Hartman JE, **Klooster K**, Ten Hacken NHT, Slebos DJ
Therapeutic Advances in Respiratory Disease 2015;9(5):251-9.

14. **The minimal important difference for the St George's Respiratory Questionnaire in patients with severe COPD**
Welling JB, Hartman JE, Ten Hacken NHT, **Klooster K**, Slebos DJ
The European respiratory journal 2015;46(6):1598-604.

15. **Bronchoscopic Coil Treatment for Patients with Severe Emphysema: A Meta-Analysis**
Slebos DJ, Hartman JE, **Klooster K**, Blaas S, Deslee G, Gesierich W, Hetzel J, Hetzel M, McNulty W, Kemp SV, Kessler R, Leroy S, Stanzel F, Witt C, Zoumot Z, Herth FJ, Shah PL
Respiration 2015;90(2):136-45.

16. **Relapse in FEV1 Decline After Steroid Withdrawal in COPD**
Kunz LI, Postma DS, **Klooster K**, Lapperre TS, Vonk JM, Sont JK, Kerstjens HA, Snoeck-Stroband JB, Hiemstra PS, Sterk PJ; GLUCOLD Study Group
Chest 2015;148(2):389-96.

17. **Oxidant-induced corticosteroid unresponsiveness in human bronchial epithelial cells**
Heijink I, van Oosterhout A, Kliphuis N, Jonker M, Hoffmann R, Telenga E, **Klooster K**, Slebos DJ, ten Hacken NHT, Postma D, van den Berge M.
Thorax 2014;69(1):5-13.

18. **Daily physical activity after bronchoscopic lung volume reduction: a pilot study**
Hartman JE, Boezen HM, Heintzbergen S, de Greef MH, **Klooster K**, ten Hacken NHT, Slebos DJ
Eur Respir J. 2012 Dec;40(6):1566-7.

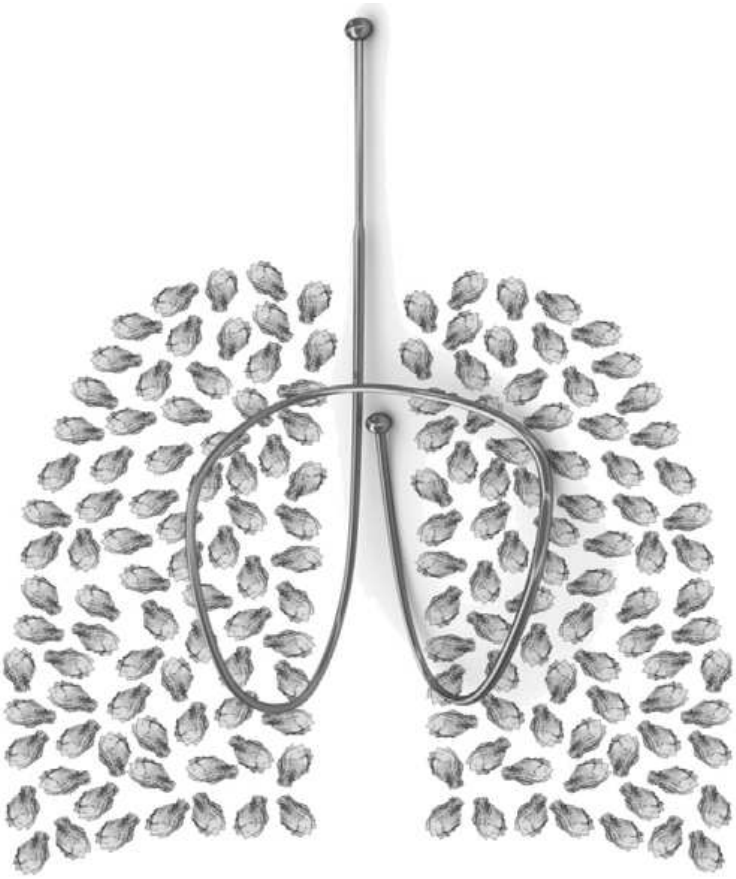
19. **The minimal important difference for residual volume in patients with severe emphysema**
Hartman JE, Ten Hacken NHT, **Klooster K**, Boezen HM, de Greef MH, Slebos DJ
The European respiratory journal 2012; 40(5):1137-41.

20. **FVC to slow inspiratory vital capacity ratio: a potential marker for small airways obstruction**
Cohen J, Postma DS, **Klooster K**, van der Bij W, Verschuuren E, Ten Hacken NHT, Koëter GH, Douma WR
Chest 2007; 132(4):1198-203.

21. **The NK-2 receptor antagonist SR 48968C does not improve adenosine hyper responsiveness and airway obstruction in allergic asthma**
Kraan J, **Klooster K**, Postma DS
Clinical and Experimental Allergy 2001; 31(2):274-8.

Curriculum Vitae

Henderika (Karin) Klooster was born on July 2nd, 1973 in Bedum, The Netherlands. She works since 1992 at the pulmonary department of the University Medical Center Groningen in the Netherlands. With over 15 years of experience as a pulmonary function technician. Since 2006 she is working as clinical research coordinator in several medical device trials in the field of bronchoscopic lung volume reduction treatments. Besides working as clinical research coordinator, she started her PhD research in July of 2013 and followed at The Graduate School of Medical Sciences in Groningen several training courses for PhD students. During her PhD she also participated in international conferences where she presented her research findings. She gave lectures during international investigator meetings. She was awarded on behalf of the Assembly on Clinical Problems of the American Thoracic Society. The abstract "Endobronchial valves for emphysema without interlobar collateral ventilation" received a Dr. Sreedhar Nair Memorial Award given for top abstracts from the National Emphysema Foundation. The manuscript of this randomized controlled trial was published in "The New England Journal of Medicine". Karin lives together with Dirk-Jan Slebos and their 5 children, Marinda Vink (1998), Stijn Slebos (1999) Kalena Vink (2000), Olivier Slebos (2002) en Jarwin Vink (2004).



Karin Klooster©

Karin Klooster was born on July 2nd, 1973 in Bedum, The Netherlands. Since 1992, she works at the pulmonary department of the University Medical Center Groningen, with over 15 years of experience as a pulmonary function technician. Since 2006 she is working as clinical research coordinator in the field of bronchoscopic lung volume reduction treatments for patients with COPD. Besides working as clinical research coordinator, she started her PhD in July of 2013. She lives together with Dirk-Jan and their childeren; Marinda (17), Stijn (16), Kalena (15), Olivier (14) and Jarwin (11). She enjoys traveling, cooking, cycling and just life.

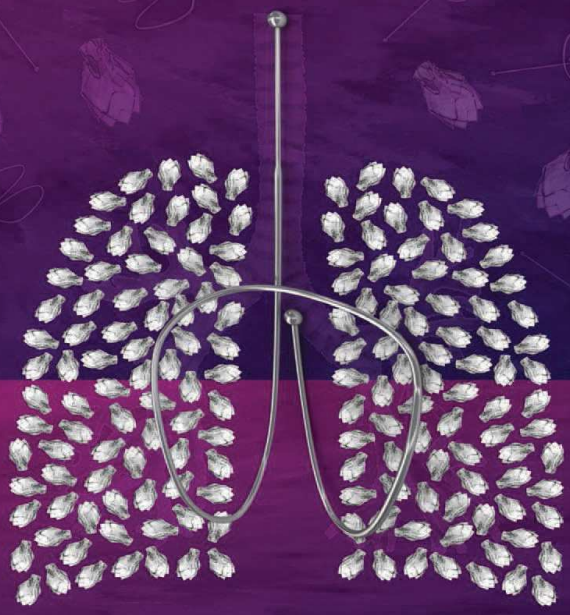
Bronchoscopic lung volume reduction

Karin Klooster

2016

Bronchoscopic lung volume reduction

A new treatment modality for patients with severe emphysema



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