# Treatment of severe




Physiology of lung volume reduction treatment
and opioids for refractory dyspnea

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# TABLE OF CONTENTS

CHAPTER 1

# General introduction

1

## 1.1 COPD

Chronic Obstructive Pulmonary Disease (COPD) is a common, incurable, but treatable, disease characterized by airflow obstruction, emphysema and chronic bronchitis [1]. Cigarette smoking is the underlying cause of COPD in up to 90% of cases in The Netherlands, but worldwide 25 to 45% of patients with COPD are never-smokers [2, 3].

Loss of small airways (< 2 mm diameter) and structural changes in small airways are the most important cause of expiratory airflow obstruction in COPD [4, 5]. Emphysema, defined as the loss of alveoli, also contributes to airflow obstruction by impaired tethering of airways in the lung parenchyma. Additionally, emphysema leads to a reduced gas exchange surface and a reduction of pulmonary capillaries [6, 7]. Furthermore, loss of elastic recoil and increased airway resistance caused by emphysema can induce static hyperinflation, which leads to an increase in end-expiratory volume and residual volume and a decrease in inspiratory and vital capacity [8].

Dyspnea and productive cough are the most common complaints in COPD. Systemic symptoms such as fatigue and cachexia can also occur, especially in more advanced disease [9]. The disease trajectory of COPD is characterized by exacerbations during which day-to-day symptoms worsen for days to weeks on end necessitating additional treatment or even hospital admission [10]. Comorbidities, such as cardiovascular disease, osteoporosis and depression, are highly prevalent in COPD [1, 9]. The combination of every day complaints, reduced exercise tolerance, exacerbations and comorbidities can severely impact quality of life for patients with COPD [11-13]. Furthermore, COPD is currently the third leading cause of mortality worldwide, with one in twenty deaths being caused by COPD [14].

Numerous pharmacological and non-pharmacological treatment modalities are available for COPD. Smoking cessation is key for patients with COPD who are smoking. Other important non-pharmacological interventions include stimulation of physical activity and education on self-management and other subjects [1, 15]. Long acting bronchodilators are the cornerstone of pharmacological management in COPD [1]. Furthermore, inhaled corticosteroids can be indicated, especially for those patients with more severe COPD and frequent exacerbations [16]. Since COPD is a heterogeneous disease, a ‘one-size-fits all approach’ is unlikely to be successful. Identification of treatable traits (patient or disease characteristics with specific therapeutic options) can help to optimize and personalize treatment (table 1: treatable traits in COPD).

## 1.2 Severe COPD

The severity of COPD is estimated from the severity of the airflow obstruction, the frequency of exacerbations and the severity of complaints the patient perceives [1]. Other characteristics that are associated with more severe disease and higher COPD-related mortality are the presence of a respiratory insufficiency, pulmonary hypertension, severe

static hyperinflation, cachexia and a higher number of comorbidities [17-21].

Refractory dyspnea or breathlessness is the most common complaint in severe COPD. It is defined as persisting complaints of dyspnea despite optimal therapy for the underlying disease and occurs in up to 94% of patients with COPD during the last year of life [22]. The presence of refractory dyspnea can have far reaching negative effects on the life of both patients and their loved ones [12].

As the term implies, refractory dyspnea can be challenging to treat. Non-pharmacological options include breathing exercises, the use of a handheld fan and oxygen therapy [1, 23]. Low-dosed opioids are the most important additional pharmacological treatment option. However, the quality of scientific evidence for opioids for this indication is considered to be low to very low [24].

**Table 1** | Treatable traits in COPD

| **Treatable traits in COPD** | **Treatment options** | |
|---|---|---|
| | ***Non-pharmacological*** | ***Pharmacological*** |
| **Pulmonary** | | |
| *Airway smooth muscle contraction* | | Bronchodilators |
| *Eosinophilic airway inflammation* | | Inhaled corticosteroids, type 2-biologicals* |
| *Chronic bronchitis* | Smoking cessation | Maintenance macrolides |
| *Frequent exacerbations* | Vaccination (influenza, pneumococ), rehabilitation | Inhaled corticosteroids, maintenance macrolides, roflumilast (PDE4-inhibitor) |
| *Infections (bronchitis, pneumonia)* | | Antibiotics |
| *Bronchiectasis* | Physiotherapy (cough technique) | Nebulized NaCl*, maintenance macrolides, antibiotics prescribed on the basis of sputum culture |
| *Cough reflex hypersensitivity* | Speech therapy | Amitriptyline*, gabapentine* |
| *Chronic respiratory insufficiency* | Oxygen therapy, non-invasive ventilation, lung transplantation | |
| *Pulmonary hypertension* | Oxygen therapy, lung transplantation | |
| *Emphysema, hyperinflation* | Bronchoscopic or surgical lung volume reduction, lung transplantation | Bronchodilators |
| *Alpha-1-antitrypsin deficiency* | | Intravenous suppletion |

**Table 1** | *Continued*

| | Treatment options | |
|---|---|---|
| **Treatable traits in COPD** | ***Non-pharmacological*** | ***Pharmacological*** |
| *Refractory dyspnea* | Handheld fan, oxygen therapy, breathlessness service | Opioids |
| **Extrapulmonary** | | |
| *Rhinosinusitis* | Nasal or sinus surgery | Nasal corticosteroids |
| *Deconditioning* | Physiotherapy, rehabilitation | |
| *Cachexia* | Diet, physical activity | Anabolic-androgenic steroids during pulmonary rehabilitation* |
| *Obesity* | Diet, bariatric surgery | |
| *Cardiovascular disease* | PCI, bypass surgery | β-blockers, ACE-inhibitors, diuretics, statins |
| *Inducible laryngeal obstruction* | Speech therapy | |
| *Anxiety, depression* | Psychological therapy | Anxiolytics, antidepressants |
| *Obstructive sleep apnea* | Weight loss, MRA, CPAP | |
| *Osteoporosis* | Minimalize steroid use, physical activity | Calcium and vitamine D suppletion, bisphosphonates |
| *Gastro-oesophageal reflux* | Reverse Trendelenburg position during sleep | Protonpomp inhibitors |
| **Behavioural and lifestyle** | | |
| *Poor inhalation technique* | Education, regular practice and check | |
| *Poor adherence to treatment* | Education, regular check up, smart inhalers | |
| *Smoking* | Coaching | Nicotin replacement therapy, varenicline, bupropion, nortriptyline* |
| *Exposure to toxic agents or allergens* | Avoidance | Desensibilisation for allergens |
| *Side-effects of other treatments* | Education | Adjust and optimize treatment |
| *Polypharmacy* | | Systematic medication evaluation |
| *Insufficient family and social support* | Support from social work | |

*PDE4 = phosphodiesterase-4; PCI: percutaneous coronary intervention; MRA = mandibular repositioning device; CPAP = continuous positive airway pressure. * Scientific literature available,*

*but not officially registered for this indication in The Netherlands. Table translated from van Dijk M, Sachs APE, Kerstjens HAM. COPD: denken in behandelbare kenmerken [COPD: working with treatable traits]. Ned Tijdschr Geneeskd. 2021 Apr 29;165:D5326. Dutch. PMID: 34346592. [3]*

## 1.3 Lung volume reduction treatment

Lung volume reduction treatments have been developed for patients with emphysema and severe static hyperinflation. The proposed mechanism for lung volume reduction treatments is better matching of the size of the lungs to the thorax containing them [25]. This leads to a reduction in static hyperinflation, improvement of airflow obstruction and improved elastic recoil of the lungs, which in turn can lead to a reduction in dyspnea, better exercise tolerance and improved quality of life [26]. However, to achieve a successful treatment, patient selection is key. Both surgical and bronchoscopic types of lung volume reduction treatment are available.

Lung volume reduction surgery was developed in the 1950's [27], but a high mortality rate prevented lung volume reduction surgery from becoming standard of care therapy for a long period of time. However, in the 1990's there was a revival of lung volume reduction surgery [28, 29], which culminated in the large, international, randomized National Emphysema Treatment Trial where bilateral non-anatomical resection of upper lobe predominant emphysema led to improvement of lung function, dyspnea, exercise capacity and survival [30]. This form of surgery is also known as classical lung volume reduction surgery. A lobectomy of the most diseased lung lobe, usually performed by video-assisted thoracic surgery, or bullectomy of a giant bullae (*i.e.* taking up ≥1/3 of the hemithorax) are other types of lung volume reduction surgery.

Bronchoscopic lung volume reduction treatments have been developed in the last two decades as a less invasive alternative for lung volume reduction surgery. Bronchoscopic lung volume reduction treatment with one-way valves and endobronchial coils are the two best-known bronchoscopic lung volume reduction treatments, and both are mentioned in the international COPD GOLD guideline as treatment option for selected patients with severe emphysema and hyperinflation [1]. In the Netherlands, treatment with one-way valves has been covered by health insurance since 2017. The goal of valve treatment is to endoscopically close off all the airways of the most emphysematous lung lobe with one-way valves (*i.e.* air can leave but not enter the lung lobe), to achieve lung volume reduction or even a complete lobar atelectasis [31]. It is essential for this treatment that there is no collateral ventilation between the target lobe and ipsilateral lobe(s) [32]. One-way valve treatment has been shown to have a positive effect on airflow obstruction, static hyperinflation, exercise tolerance, and quality of life [26, 32-35].

Treatment with endobronchial coils is only performed within clinical trials in the Netherlands. Endobronchial coil treatment is a non-blocking technology where shape-memory nitinol coils are placed in the two most diseased lung lobes [36]. This treatment is not dependent on

the absence of collateral ventilation. The proposed mechanism of action for coil treatment is a reduction in residual lobar volume by improved tissue tension and airway tethering [37]. A positive effect on pulmonary function, exercise tolerance and quality of life has been demonstrated in patients with severe hyperinflation [38].

## 1.4 Outline of this thesis

There are two main aims for this thesis. The first aim is to increase physiological insight in lung volume reduction treatments, in order to improve and potentially expand patient selection and optimally balance the chance of successful treatment with the chance of complications or unwanted side effects. The second aim of this thesis is to improve treatment of refractory dyspnea in COPD by investigating low dosed opioids for this indication.

In **chapter 2** we review recent developments in the treatment for severe stable COPD. The available literature on advanced treatment options is discussed by identification of treatable traits.

For **chapter 3** we performed a meta-analysis on the effect of lung volume reduction surgery and one-way valve treatment on diffusing capacity and gas exchange. In addition, we review which factors possibly influence change in diffusing capacity and gas exchange after lung volume reduction treatment and which diagnostic tests could help to reliably evaluate this.

In lung volume reduction treatments, a very low diffusing capacity is seen as a risk factor for a higher mortality rate and more serious complications. In **chapter 4** we performed a retrospective analysis of the outcomes of endobronchial valve treatment in patients with a very low diffusing capacity. We compared these outcomes to a matched historical control group.

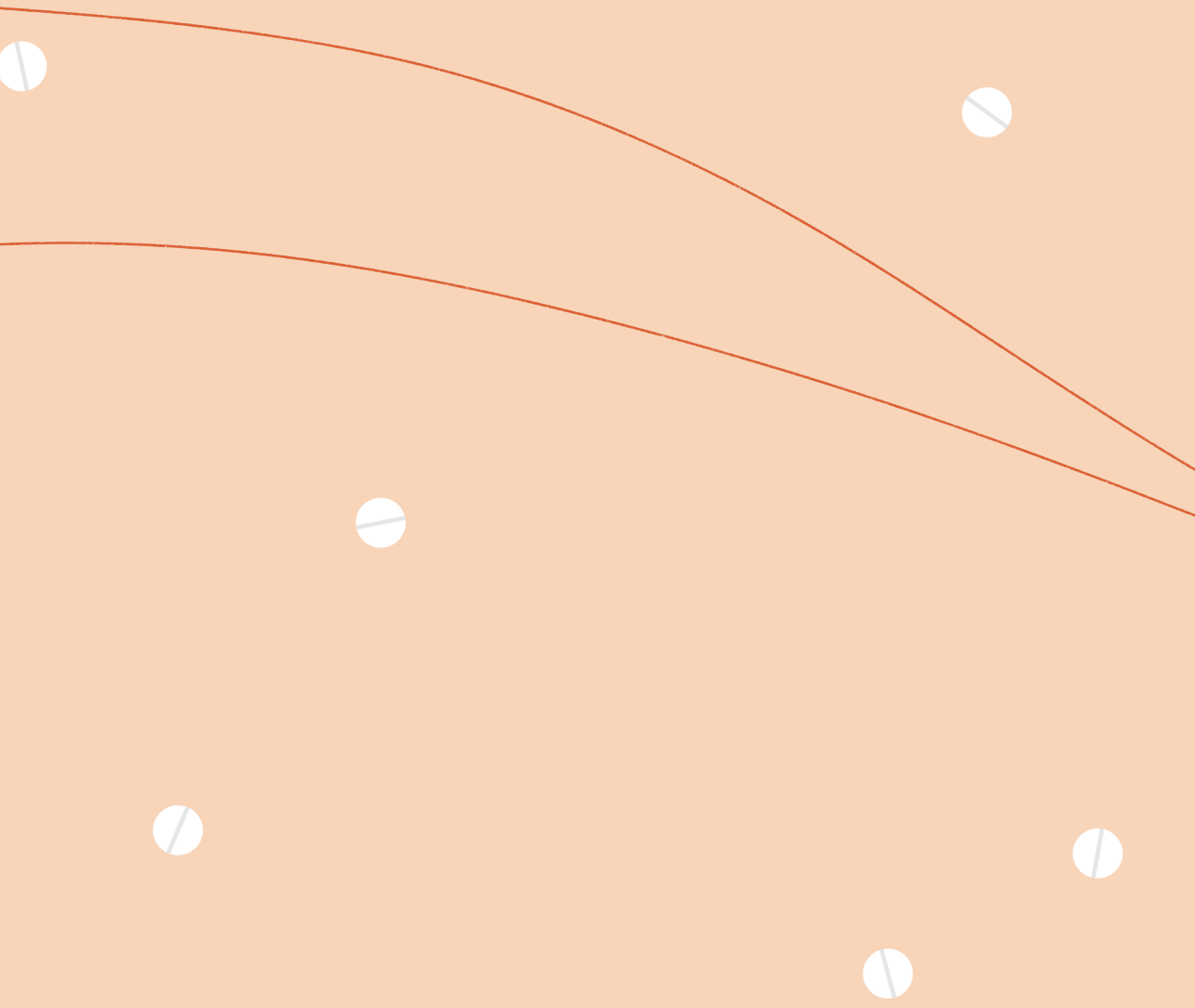
In **chapter 5 and 6** we investigate change in dynamic hyperinflation after bronchoscopic lung volume reduction treatment. The effect of lung volume reduction treatment on static hyperinflation is very clear, but this is not the case for dynamic hyperinflation. In **chapter 5** dynamic hyperinflation was measured before and after coil or valve treatment with a manually paced tachypnea test. In **chapter 6**, three different diagnostic test to measure dynamic hyperinflation are compared in a group of patients with severe COPD who underwent endobronchial coil treatment.

**Chapter 7** describes the first in human experience of placement of a new size endobronchial valve (Zephyr® endobronchial valve, 5.5-LP), which was developed to accommodate for wider airways with a short length. In this single center prospective study the safety and effectiveness was evaluated in patients who were treated with this new size valve.

The most common complication of bronchoscopic lung volume reduction with endobronchial valves is a pneumothorax. **Chapter 8** consists of an expert statement on this subject.

Amongst others, risk assessment, prevention and optimal treatment of pneumothorax associated with one-way valve treatment are discussed. A modified Delphi structure was used to evaluate the expert opinion in a systematic way.

Originally, the intention was to describe the outcomes of our multi-center, double blind, randomized clinical trial 'Morphine or Fentanyl for refractory dyspnea in COPD [MoreFoRCOPD]' in **chapter 9**. However, due to the Corona pandemic the inclusion of patients in the MoreFoRCOPD trial has sustained significant delay. Therefore, we have now chosen to describe the study design of MoreFoRCOPD, where we investigate whether low-dosed morphine and fentanyl are more effective to treat refractory dyspnea in COPD than placebo. In addition to the description of the study design, this chapter also contains a systematic review of the effect of opioids on dyspnea, quality of life and health status in COPD.



CHAPTER 2

# Treatment of severe stable COPD: the multidimensional approach of treatable traits

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## Abstract

Now that additional treatment options for severe chronic obstructive pulmonary disease (COPD) have emerged in recent years, patients with severe COPD should not be left in the rather hopeless situation of "there is nothing to improve" any more. Inertia or fatalism is a disservice to our patients. Ranging from advanced care planning to quite intense and demanding therapies such as multidisciplinary pulmonary rehabilitation, (endoscopic) lung volume reduction, chronic noninvasive ventilation and lung transplantation, caregivers should try to provide a personalized treatment for every severe COPD patient. In this review, we aim to describe the multidimensional approach to these patients at our center along the lines of treatable traits leading to specific additional treatment modalities on top of standard care.




## Introduction

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death worldwide [1], and the number of patients with severe end-stage COPD is still increasing. These patients often experience disabling symptoms of dyspnea, fatigue, bad sleep, morning headache and loss of energy levels, severely impacting on their health-related quality of life (HRQoL). For a long period of time, there have been few effective treatment options for the majority of these patients. However, during the last decade, multiple treatment modalities have become more widely available. To identify the right patients for the right therapy, we believe in the concept of identifying "treatable traits" for patients, *i.e.* therapeutic targets identified by "phenotype" or "endotype" recognition [10, 39, 40]. An individual assessment of the patient helps to identify a set of treatable problems specific to this patient, and subsequently a personal treatment plan can be developed and implemented [41]. Since severe COPD is a complex and heterogeneous disease, identifying treatable traits can lead to a more effective and personalized treatment.

We aim to describe and review recent developments in the treatment of severe stable COPD, on top of standard therapy such as optimal pharmacological treatment (according to current Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines) [1], smoking cessation, influenza vaccination and treatment of common comorbidities such as rhinitis. We will do so according to identification of treatable traits (figure 1) leading to additional treatment modalities in very severe COPD. Illustrated by a case study, we will incorporate these treatment options into a multidimensional approach. This is an approach that we have developed and is used by our dedicated severe COPD team at the University Medical Center Groningen. Written informed consent was obtained for the use of medical data for the case study, and all data were treated with confidentiality according to Good Clinical Practice guidelines.

## Case study

A 55-year-old woman, with COPD GOLD classification IV/D, osteoporosis and an anxiety disorder, was referred to our outpatient clinic for assessment (table 1). She was very well motivated for additional treatment options improving her HRQoL. She was evaluated during a 1-day assessment consisting of a doctor's consultation, full lung function testing, high-resolution computed tomography (HRCT) scan, arterial blood gas analysis at room air and a 6-min walk test, and consultation with a respiratory nurse and respiratory physiotherapist. The assessment revealed that she suffered from severe dyspnea, present in rest and increasing with exercise (modified Medical Research Council (mMRC) [42] score 3). She complained of headaches and difficulty sleeping. Furthermore, she experienced exacerbations frequently (one course of prednisone each month prescribed by the general practitioner). She had a history of 37 pack-years of smoking, but had quitted smoking 5 years ago. She was currently being treated with formoterol 24 µg twice daily, beclomethasone small particles 200 µg twice daily and tiotropium 18 µg every day, all of which she used correctly. She also used alprazolam for anxiety and promethazine to help her sleep. Physical examination showed a cachectic woman in respiratory distress at minimal exercise. Her lung function tests showed that she had a severe airflow obstruction and severe hyperinflation. Arterial blood gas analysis showed a total respiratory failure. Her blood α1-a-antitrypsin level was 1.4 $g \cdot L^{-1}$. She was on long-term oxygen therapy (LTOT). She could walk only 125 m on the 6-min walk test. The HRCT scan revealed centrilobular emphysema in a heterogeneous distribution, with more extensive destruction in both lower lobes. Both major fissures appeared to be complete; the minor fissure was incomplete. Furthermore, the HRCT scan showed moderate central and peripheral bronchopathy with mucus plugging (figure 2).

**Table 1** | Characteristics of the presented case

| **Case, woman, 55 years old** | |
|---|---|
| BMI, $kg/m^2$ | 17 |
| $FEV_1$, L | 0.42 |
| $FEV_1$, % of predicted | 14 |
| FVC, L | 1.97 |
| FVC, % of predicted | 53 |
| $FEV_1$/FVC, % | 21 |
| TLC, % of predicted | 109 |
| RV, % of predicted | 211 |
| RV%TLC | 72 |
| $DL_{CO}$, % of predicted | 29 |
| pH, at room air | 7.40 |
| $PaCO_2$, kPa (mmHg), at room air | 7.2 (54) |
| $PaO_2$, kPa (mmHg), at room air | 6.0 (45) |
| $HCO_3$-, mmol/L, at room air | 34 |
| 6MWD, m | 125 |

*BMI: Body Mass Index, $FEV_1$: forced expiratory volume in 1s;FVC: Forced Vital Capacity; TLC: Total Lung Capacity; RV: Residual Volume; $DL_{CO}$: diffusing capacity of the lung for carbon monoxide; $PaCO_2$: arterial carbon dioxide tension; $PaO_2$ arterial oxygen tension; $HCO_3$: bicarbonate; 6MWD: 6 min walk distance.*

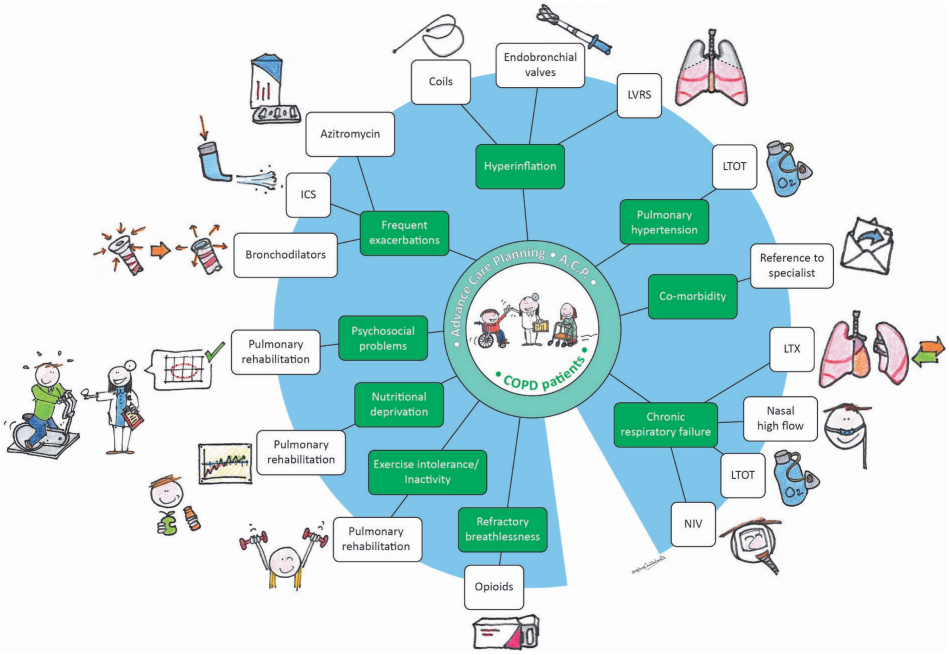



*Figure 1: Overview of treatable traits in advanced COPD with posssible treatment options. AATD: α1 antitrypsin deficiency; LVRS: lung volume reduction surgery; LTOT: Long-term oxygen therapy; LTx: lung transplantation; NIV: noninvasive ventilation; ICS: inhaled corticosteroids.*

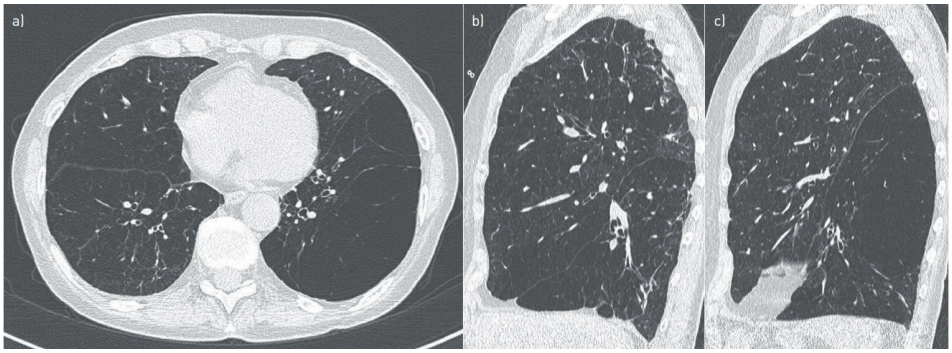



*Figure 2: HRCT scan showing severe epmhysema predominantly in the lower lobes and moderate central and peripheral bronchopathy with mucus pluggin. Both major fissures appear to be complete.*

## Pulmonary treatable traits in severe COPD

### *Treatable trait: frequent exacerbations*

Exacerbations of COPD profoundly impact the patients' health status, functional capacity and lung function [43]. Especially severe exacerbations (exacerbations requiring hospitalization) have a significant clinical and socioeconomic impact. Furthermore, having an exacerbation is an important risk factor for further exacerbations, and repeated exacerbations are associated

with an increased mortality risk [44]. Therefore, it is important to prevent exacerbations by targeting modifiable risk factors ("treatable traits") for readmission, rather than treating exacerbations only when they occur. Besides the well-known pharmacological options with long-acting bronchodilators in patients with severe COPD, the following pharmacological treatment options are of interest. Firstly, in patients with frequent exacerbations, increased blood eosinophilic level increases the likelihood of reducing exacerbation risk with inhaled corticosteroids (ICS) [17, 45-47], thus probably representing a modifiable risk factor and treatable trait. It should be noted that the relationship between the eosinophil count and reduction in exacerbation rate is a continuous one, and therefore there is no clear cut-off point for deciding whether or not the patient could benefit from using ICS. Of note, there is no evidence that chronic use of oral corticosteroids as maintenance therapy effectively prevents exacerbations [48, 49], while the side-effects of prolonged prednisolone, such as steroid myopathy [50] and increased risk of pneumonia [51], are substantial.

Secondly, Roflumilast (a phosphodiesterase-4 inhibitor acting as an anti-inflammatory drug) has been shown to reduce the risk of severe exacerbations in patients with severe COPD and symptoms of chronic bronchitis, who have repeated exacerbations and are already on maintenance therapy with ICS, long-acting β-agonists and long-acting muscarinic antagonists [52, 53]. However, its use might be limited by its frequent side-effects, limiting the effect on HRQoL or symptoms [54]. A more attractive alternative may be the use of macrolides (with both anti-inflammatory and anti-bacterial action) used prophylactically to reduce the rate of COPD exacerbations [55-57]. Disadvantages (antibiotic resistance, side-effects) should be balanced against expected benefits, and further studies are required to determine the optimal treatment regime and duration, particularly in patients with more severe COPD [58]. Furthermore, in most EU countries, the prescription of macrolides maintenance therapy is off-label.

Importantly, several non-pharmacological treatment options might be useful in preventing exacerbations. Pulmonary rehabilitation has been shown to reduce the number of exacerbations, healthcare utilization and healthcare costs [59]. However, the direct availability of pulmonary rehabilitation post hospitalization might be a problem because of limited resources. In patients with very severe COPD exacerbations, requiring acute noninvasive ventilation (NIV) during their exacerbation, and persistent severe post-exacerbation hypercapnia, continuing NIV nocturnally at home has been shown to increase the time to the next exacerbation and reduce subsequent exacerbation rate [60]. Chronic home nasal high-flow therapy (nHFT) is another promising option to reduce exacerbation rates in patients with frequent exacerbations [61], but evidence is limited and further trials are needed. Two bronchoscopic treatments have shown potential for exacerbation rate reduction in COPD. Targeted lung denervation (TLD) is an experimental bronchoscopic treatment disrupting parasympathetic nerves in the airways. In a recent phase II multicentre trial, the exacerbation rate during 3 to 6 months follow-up was 17.1% for the group receiving TLD *versus* 36.6% in the group receiving sham treatment ($p$=0.08) [62]. The underlying

pathophysiological mechanism that leads to exacerbation reduction is not entirely clear but could be analogous to long-acting muscarinic antagonists, since both treatments have an anticholinergic effect. Currently, the effect of TLD on exacerbation frequency is being investigated further in a phase III multicentre sham-controlled trial (Clinical trials ID: NCT03639051). In the multicentre LIBERATE trial, patients with severe COPD and hyperinflation were randomized to receive either bronchoscopic lung volume reduction treatment with endobronchial valves or standard care. During 12 months follow-up there was a trend towards fewer exacerbations in the treatment group compared to the control group (23% *versus* 30.6%, $p$=0.053) [33]. However, treatment with endobronchial valves is only suitable for carefully selected patients with severe emphysema and hyperinflation. The above-mentioned non-pharmacological treatment options will be discussed further in the following sections.

***Treatable trait: hyperinflation***

Lung volume reduction treatment has been shown to be a highly effective therapy for selected patients with advanced emphysema and severe hyperinflation. By reducing hyperinflation, the function of the diaphragm and chest wall mechanics are improved, expiratory airflow increases and gas exchange can improve [63]. Historically, lung volume reduction was performed surgically, which is most beneficial in patients with upper lobe-predominant emphysema. Surgery is effective in some patients and shows improvement in lung function and quality of life [26]. However, the procedure is associated with risk of post-operative mortality and adverse events such as prolonged air leak. Therefore, in recent years, less invasive bronchoscopic lung volume reduction (BLVR) techniques have been developed and investigated thoroughly, amongst others in our center, to achieve lung volume reduction in patients with severe emphysema and hyperinflation [64]. In general, patients with severe COPD and hyperinflation (residual volume (RV) >175% predicted or RV/total lung capacity (TLC) ⩾0.58) who are highly symptomatic despite optimal treatment are good candidates for BLVR [36]. To evaluate the possible treatment options in these patients, an HRCT scan should always be performed to assess the destruction of lung tissue, heterogeneity of emphysema and the fissure completeness.

Currently, the most important bronchoscopic options are treatment with one-way valves or endobronchial coils; both treatments are currently recommended in the COPD GOLD guidelines [1, 36]. Treatment with endobronchial one-way valves has been proven to be effective in multiple randomized controlled studies, with clinically meaningful benefits in lung function, dyspnea, quality of life and exercise tolerance [32, 34, 35, 65]. Valves are placed in all (sub)segments of a target lobe to create volume reduction of this lobe. However, the treatment is only effective in patients with absence of interlobar collateral ventilation, otherwise no atelectasis of the treated lobe can occur. The presence of collateral ventilation is predicted by calculating the fissure completeness score on HRCT using quantitative computed tomography (CT)-analysis [66] and functionally measured during

bronchoscopy with the Chartis system® (PulmonX Inc., Redwood City, CA, USA) [67]. If a patient is not eligible for treatment with endobronchial valves, for example due to lack of a good treatment target lobe or incomplete fissures, treatment with endobronchial coils may be considered [38, 64, 68]. Endobronchial coil placement has been shown to elicit sustained improvements in a patient's quality of life and a decrease in residual volume. However, research is ongoing to predict the optimal responders; treatment appears to be more successful in patients with an even higher baseline RV (>200% predicted), a higher emphysema destruction score and absence of airway disease [36]. Another treatment option in patients who are not eligible for valve treatment is bronchoscopic thermal vapor ablation. With this treatment, heated water vapor is delivered to emphysematous areas to induce an inflammatory reaction, which leads to lung volume reduction. This treatment has resulted in improvements in lung function and quality of life in patients with upper lobe-predominant emphysema [69].

### *Treatable trait: chronic respiratory failure*

#### *Long-term oxygen therapy*

Chronic hypoxaemic respiratory failure is an indication for LTOT. In the Netherlands, it is estimated that at least 10 000 patients receive LTOT each year (62/100 000 inhabitants) and 2000 new patients are prescribed LTOT annually. The evidence for LTOT in COPD stems from two landmark trials performed over 40 years ago showing that LTOT prolonged life in patients with severe resting hypoxaemia *versus* placebo in one trial, and if used continuously *versus* only nocturnally in the other trial [70, 71]. However, these trials were performed in very severe hypercapnic COPD patients who would probably be treated today with chronic NIV. Since then, several trials have been performed to investigate whether supplemental oxygen improves outcomes in patients with moderate hypoxaemia [72], exercise-induced desaturations and post-exacerbation hypoxaemia, and in those receiving palliative care. There may be some positive indications, for example for supplemental oxygen during exercise that improves exercise endurance and maximal exercise capacity in COPD patients with exercise-induced hypoxaemia [73-75], but there is no evidence that these strategies contribute to long-term clinically relevant benefits [76]. There is some rationale that particularly nocturnal hypoxaemia contributes to the development of secondary pulmonary hypertension and right heart failure, leading to a worse prognosis. The INOX trial aims to answer the question whether nocturnal oxygen provided for a period of 3 years decreases mortality or delays the prescription of LTOT in patients with COPD not qualifying for LTOT but who do have significant nocturnal arterial oxygen desaturation [77]. In our team, we evaluate oxygen therapy according to the British Thoracic Society (BTS) guidelines [78] (due to be reviewed in 2020) and additionally prescribe it during pulmonary rehabilitation in patients with exercise-induced desaturations. Of note, the way LTOT is prescribed, with a mobile device that allows patients to be ambulatory for a considerable amount of time, is extremely important in keeping patients engaged in society with optimal HRQoL.

*Chronic noninvasive mechanical ventilation*

When patients develop type II chronic hypercapnic respiratory failure (arterial carbon dioxide tension ($PaCO_2$)>6.0 kPa), long-term NIV should be offered [79]. Chronic NIV in COPD has long been the subject of debate as the evidence was conflicting [80]. With the introduction of high-intensity NIV, which is defined as specific ventilator settings aimed at achieving normocapnia or the lowest $PaCO_2$ values possible [81], both physiological and clinical benefits of long-term NIV have been shown in patients with COPD [60, 82-88]. Chronic home NIV has been shown to improve survival, HRQoL, exercise tolerance and exacerbation frequency especially in patients with severe hypercapnia, both in a chronic stable state [85] and with persistent severe hypercapnia after an exacerbation [60]. Moreover, combining nocturnal NIV with a pulmonary rehabilitation program augments the benefits of the rehabilitation, and this is also the case in patients with moderate hypercapnia [83, 84]. In our hospital, NIV is provided by our dedicated home mechanical ventilation team, who carefully initiate, monitor and follow-up these patients, sometimes with home visits. This dedicated approach, using an NIV setting with moderate to high pressures and a back-up respiratory rate matching the patient's respiratory rate during sleep and targeted at a substantial reduction of $CO_2$, has resulted in successful outcomes with excellent compliance rates [84, 89, 90]. However, despite this approach, not all hypercapnic patients benefit from NIV. Future research should focus on factors that predict benefit so that patients likely to gain most advantage can be selected and NIV settings optimally individualized.

*Nasal high-flow therapy*

nHFT supplies heated, humidified and oxygen-enriched air at high flow rates through a nasal cannula. Because the air is provided through an open system with a nasal cannula, it is relatively easy to apply and suggested to be comfortable for patients. Currently, there is growing interest in home nHFT for the treatment of chronic respiratory failure in patients with COPD [91, 92]. Although there are some longer-term clinical studies investigating nHFT in severe COPD, the evidence is still limited, and nHFT is not standard care in many countries [93]. In hypoxaemic COPD patients, there is evidence that nHFT lowers the exacerbation rate and improves dyspnoea, HRQoL, $PaCO_2$ and 6 min walk distance, although the study was performed in a poorly defined patient group and the exacerbations were patient reported [61]. In hypercapnic COPD patients, there are some preliminary data that indicate that nHFT might be beneficial [94, 95], but a recent randomized controlled trial (RCT) showed only non-inferiority and no clear advantage of nHFT compared to NIV [96, 97]. As nHFT might also act positively on lung airway clearance, it would be interesting to investigate the efficacy of nHFT in the treatment of COPD exacerbations [98] and in promoting clinical stability and prevention of re-exacerbations over an extended period of time. A key problem in the application and implementation of nHFT is that the mechanisms underlying the technique are diverse, and its effect on patients in real-life situations is not clear. Furthermore, the appropriate way to apply (how many hours, day or night use?) nHFT is unknown, demonstrating the necessity of new studies. In our center, we currently provide

long-term home nHFT in clinical trials only (ClinicalTrials.gov NCT03564236).

### *Treatable trait: α1 antitrypsin deficiency*

α1 antitrypsin deficiency (AATD) is a genetic disorder caused by a great variety of mutations in the SERPINA-1 gene. If both alleles of the gene are mutated, this can lead to AATD, with Type ZZ being the most common genotype in severe AATD [99]. The current GOLD guidelines advise screening of every COPD patient for AATD (especially in regions with a high prevalence), and not only the typical patient who is diagnosed with COPD at an early age and has lower lobe-predominant emphysema [1]. However, in clinical practice it appears that only a minority of patients with COPD are tested for AATD [100]. The first diagnostic test to diagnose AATD is usually measurement of α1 antitrypsin levels in blood. An α1 antitrypsin level lower than 1.1 $g \cdot L^{-1}$ is suggested as the threshold for further testing, which consists of either protein phenotyping or genotyping [101]. Notably, forced expiratory volume in 1 s ($FEV_1$) and diffusing capacity can behave differently in AATD, and a decline in either one can be the first indication of rapid progression of the disease. Therefore, annual follow-up of both spirometry and gas transfer is important to monitor the disease [101]. AATD can also have extrapulmonary manifestations, most importantly liver disease, for which additional testing should be considered [102]. Furthermore, family members can be affected, and screening for AATD should be offered to them [1].

Since AATD is rare, patients should be referred to an expert center for management [1]. Studies investigating AAT replacement therapy have demonstrated some effect in reducing the rate of decline in $FEV_1$ in observational studies (9 to 22 mL lower reduction in $FEV_1$ per year compared to controls) and progression of emphysema measured by CT densitometry in RCTs [101]. It is important to note that replacement therapy is a high-cost treatment, and availability may vary among different countries.

### *Treatable trait: pulmonary hypertension*

Development of pulmonary hypertension (PH) in COPD is common and has a negative impact on exercise capacity, prognosis and survival [20]. The majority of COPD patients who develop PH have a mean pulmonary artery pressure of between 20 and 35 mmHg [103]; only 3–4% of patients have a mean pulmonary artery pressure >35 mmHg [20, 103]. It has been suggested that there is a pulmonary vascular phenotype of COPD patients. These patients have less severe airflow limitation, more severe hypoxaemia, very low diffusing capacity and cardiovascular exercise limitation [104, 105]. It is recommended that COPD patients should be evaluated for PH when it has an impact on patient management, *i.e.* referral for lung transplantation, treatment of left heart failure or inclusion in clinical trials [106].

Although chronic hypoxaemia is an important contributor to PH in COPD, other factors may play a role and need to be elucidated. For example, it has been shown that vascular lesions associated with idiopathic pulmonary arterial hypertension may also be present in

patients with COPD and PH [107]. Unfortunately, since it is unclear what factors contribute to the vasculopathy in COPD patients with PH, identifying treatments to reverse PH in COPD remains challenging and merits further investigation.



The only recommended therapy to influence PH in COPD is long-term oxygen therapy [108]. Oxygen therapy used >15 h per day obviated an increase in pulmonary artery pressure, whereas oxygen therapy used >18 h per day reduced mean pulmonary artery pressure [109, 110]. In COPD patients with PH, there is no firm evidence that improvement of pulmonary hemodynamics with vasodilator therapy results in significant improvement of symptoms and exercise tolerance [111-114]. Treatment with calcium channel blockers is not advised, because of the potential deterioration of gas exchange [112, 115]. For endothelin receptor antagonists and phosphodiesterase inhibitors there are only a few and rather small randomized trials. Meta-analyses have shown a beneficial effect on pulmonary haemodynamics, but there are conflicting data on the effect on exercise tolerance and disappointing results on symptoms and quality of life [116, 117]. It is important to identify additional comorbidities leading to PH such as left heart failure, chronic thromboembolic disease and obesity/obstructive sleep apnoea. It is currently unknown whether chronic NIV reduces pulmonary artery pressures in COPD. NIV has been shown to reduce pulmonary artery pressure [118, 119], but only in a group of obesity hypoventilation patients. Furthermore, there is some evidence that lung volume reduction treatment might reverse PH, but the current evidence is weak and only from very small studies [120].

***Treatable trait: extrapulmonary (co)morbidities***

*Exercise intolerance/deconditioning/under- or overweight/treatable behavior*

It is commonly recognized that COPD does not only concern the respiratory system. Comorbid conditions often contribute to the phenotype and should therefore be targeted by appropriate therapies. Pulmonary rehabilitation, described as “a comprehensive intervention based on a thorough patient assessment followed by patient tailored therapies that include, but are not limited to, exercise training, education, and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviors” [121], has clearly been shown to increase exercise performance, reduce breathlessness and improve quality of life compared to usual care in patients with COPD [59]. In the Netherlands, different levels of reactivation and rehabilitation programs are available for COPD patients. Depending on the GOLD stage, patients can receive supervised exercise training in primary care if the patient’s main goal is to improve physical performance. Multidisciplinary outpatient rehabilitation programs are offered and organized in hospitals and nursing homes. For the more complex patients interdisciplinary in- and outpatient rehabilitation programs are available in specialized rehabilitation centers and paid for by all insurers. Referral for pulmonary rehabilitation is indicated for patients who experience problems in multiple domains despite optimal standard treatment. In order to receive a

personalized rehabilitation program, a thorough assessment focusing on the physical, psychological and nutritional status of the patient has to be performed before the start of the rehabilitation program [122]. In our rehabilitation center, indications for other COPD-related treatments like NIV and BLVR are all addressed during the assessment. Several aspects are of importance in the rehabilitation of very severe COPD patients. To increase exercise tolerance in these patients, strength training instead of endurance training is preferable [123]. Strength training has been shown to be equally effective as endurance training but is better tolerated due to a lower ventilatory demand. A more recent therapy is neuromuscular electrostimulation, which gives muscle contractions of the quadriceps or gastrocnemius without increase of ventilation. This therapy has been shown to improve muscle strength and endurance capacity [124]. The role of the addition of inspiratory muscle training (IMT) is controversial [121]; more recent studies failed to demonstrate an additional benefit on exercise tolerance, quality of life or dyspnoea [125, 126], and IMT training is quite burdensome for severe COPD patients. Therefore, we do not use this as regular care in our rehabilitation program for severe COPD. Ventilatory assistance during exercise (with NIV or nHFT) has been shown to improve exercise capacity and endurance [127-133]. However, assisted exercise training is quite cumbersome, and as studies have not shown long-term clinically worthwhile benefits on eventual unassisted exercise capacity and patient-related outcome measures, these assistance modes of training are not widely used. Malnourishment and cachexia are seen mainly in (very) severe COPD and are important risk factors for mortality [134]. Treatment requires an interdisciplinary approach, since it is a problem that overlaps domains. Next to the dietary intervention, a physician is needed to diagnose and treat related comorbidities and prescribe anabolic steroids in selected patients [135]. A physiotherapist is needed to appoint a training modality that does not lead to further muscle loss, and a psychologist may be needed to diagnose relevant barriers and beliefs. Surprisingly, a systematic review investigating effects of a wide range of add-on interventions to exercise training showed that there was rarely an additional effect on exercise capacity in COPD. However, as suggested by the authors, this may very well be the result of a “one size fits all” approach when selecting patients for participation in trials and probably underscores the importance of selecting suitable add-on therapies on the basis of treatable traits [136].

*Sleep disordered breathing*

The prevalence of sleep apnoea syndromes in COPD equals that of the population, although reported prevalence varies widely also according to disease stage [84, 137, 138]. Nevertheless, obstructive sleep apnoea in COPD can be considered an important treatable trait, as treatment with continuous positive airway pressure has been shown to improve survival in patients with severe hypoxaemic COPD [139]. As symptoms of excessive daytime sleepiness can be confounded by COPD symptoms [140, 141], we recommend performing a sleep study in the evaluation of a severe COPD patient, irrespective of symptoms of daytime sleepiness. Once patients have concomitant cardiovascular comorbidities, central sleep

apnoea (CSA) can often be identified, but treatment of CSA is in general more difficult. Importantly, COPD patients might develop nocturnal rapid eye movement (REM)-related hypoventilation caused by diaphragm malfunctioning due to its disadvantageous position. This might be confused for central hypopneas. However, pathophysiologically, the cause and thus treatment is completely different: when non-hypercapnic CSA due to heart failure co-exists, the treatment should focus on stabilization of periodic breathing; REM-related hypoventilation due to diaphragm malfunctioning is best treated with ventilatory support. It has, however, never been shown that initiating NIV for isolated nocturnal hypoventilation is worthwhile [142]. Therefore, it is recommended to start NIV in COPD once daytime hypercapnia develops [79].

***Optimal treatment of treatable traits: what if it is not enough?***

Unfortunately, despite optimal treatment of treatable traits, some patients are still severely impaired. For a highly selected group of these patients, lung transplantation may be an option. Furthermore, every patient with advanced COPD could potentially benefit from a multimodality treatment for refractory dyspnea and advance care planning (ACP).

*Lung transplantation for COPD*

In our center, approximately 40% of the lung transplantations performed are for COPD. We would like to stress that a multidisciplinary approach in severe COPD is important to optimally time placement of patients on the waiting list for lung transplantation. In order to stratify who is in the window for lung transplantation, looking for treatable traits to optimize the clinical condition, prognosis and quality of life is a prerequisite in this group of patients for several reasons. Successful reduction of exacerbation frequency, pulmonary rehabilitation, NIV, lung volume reduction treatment or a combination of these might withhold a COPD patient to be referred for a lung transplantation. On the other hand, if there are no treatable traits or the interventions are ineffective, a patient should be evaluated and listed in an earlier phase. In other words, assessment and treatment of treatable traits should be seen in the light of the urgency and likelihood of lung transplantation in COPD. Although the majority of lung transplants annually are still for COPD, the introduction of the Lung Allocation Score (LAS) [143] in the USA and Europe resulted in an increased time for COPD patients (with mostly a low LAS score) on the waiting list [144]. This is mainly due to the limited ability to predict length of survival when patients are screened. In COPD patients, evaluating treatable traits might result in better timing of listing for lung transplantation. Clinical deterioration under optimal treatment of traits might emphasize the need for a lung transplantation, mirrored by a higher LAS and a shorter waiting time. Future studies are needed to support this. The majority of patients who undergo lung transplantation have a good 1-year and long-term survival after lung transplantation [145]. Successful recovery post lung transplantation may be attributed to the potential of pulmonary rehabilitation, but randomized trials are lacking to support this [146]. In our rehabilitation center, there is currently a trial investigating the effect of rehabilitation post transplantation. Despite

good overall survival, the necessity of immunosuppressive drugs after lung transplantation results in comorbidities like chronic kidney failure, hypertension, diabetes, hyperlipidaemia, increased risk of infection and malignancies [145].

*Refractory breathlessness*

In advanced COPD, breathlessness is common despite optimal standard treatment and even with the advanced treatment options proposed above [147]. Amongst other things, breathlessness can lead to a reduced HRQoL, anxiety and social limitations [12]. Therefore, we should always consider additional non-pharmacological and pharmacological options to relieve refractory dyspnoea. Since breathlessness is a complex symptom, a combination of interventions is often needed to achieve an optimal result.

A relatively recent development is the so-called "Breathlessness service". This intervention addresses multiple domains: "breathing" (*i.e.* dysfunctional breathing), "thinking" (*i.e.* misconceptions, anxiety) and "functioning" (*i.e.* reduction in physical activity, self-isolation) [148]. Breathlessness services take place in the outpatient ward or at home and are usually carried out by specialist nurses or physiotherapists for a duration of 2–12 weeks. RCTs investigating these breathlessness services have shown a reduction in dyspnea sensation and an increased sense of mastery (measured by the Chronic Respiratory Questionnaire) [148]. An easy to use help might be a hand-held fan; there is some evidence that this provides benefit in the treatment of breathlessness [23]. A systematic review showed a positive effect of low-dose opioids on breathlessness in COPD, with moderate-quality evidence for the use of systemic opioids and low-quality evidence for the use of nebulized opioids [149]. However, physicians may still be hesitant to prescribe opioids [150]. Benzodiazepines and antidepressants have not been shown to have a positive effect on breathlessness, but may be indicated in case of depression or anxiety [151].

*Advance care planning*

ACP is an intervention to enable patients to define goals and preferences for future medical treatment and care, and to discuss, record and review these preferences if appropriate [152]. There are indications that ACP can increase quality of life, improve communication between patient and healthcare giver and improve the likelihood of care being delivered in accordance with the patient's preference [153].

Despite the fact that advanced COPD is associated with a high mortality rate, a high burden of physical and psychological symptoms and reduced HRQoL, only a minority of patients receive any form of ACP [154, 155]. Numerous barriers to start ACP have been identified. Barriers can be patient related (*e.g.* unpredictable disease course), healthcare professional related (*e.g.* fear of taking away patients' hope) or system related (*e.g.* perceived time constraints) [156]. Important topics to address in COPD are the unpredictable disease trajectory, prognosis, fear of breathlessness and suffocating, palliative treatment of symptoms, concerns about dying and preference of site for terminal care [157].

Although even a single conversation can lead to improved end-of-life care communication [158], ideally, ACP is an ongoing conversation between patient and healthcare giver. Furthermore, ACP is a process that should be directed by the patient but needs collaboration of pulmonologists, respiratory nurses, general practitioners and home care teams.



Since care systems vary widely among countries, there may not be one ideal way to organize ACP for COPD patients. Although we recognize that ACP should be discussed preferably at the outpatient clinic, in our current practice, ACP conversations are mostly initiated during or after hospital admissions for severe COPD. Nevertheless, there is a positive development where ACP is integrated in the pulmonary rehabilitation program and, for example, in the long-term care provided by the home mechanical ventilation center when patients are initiated on NIV. In the coming years, these initiatives need to be further extended.

***Summary: the multidimensional treatment approach***

Now that additional treatment options for severe COPD have emerged in recent years, patients with severe COPD should not be left in the rather hopeless situation of "there is nothing to improve" anymore. Inertia or fatalism is a disservice to our patients. Ranging from ACP to quite intense and demanding therapies such as NIV and lung transplantation, caregivers should try to provide a personalized treatment for every severe COPD patient. In our center, we aim to use a multidimensional approach for the patients, since one or more treatment options are always available (table 2). Furthermore, treatment options should be discussed with the patient and re-evaluated and reconsidered over time. Evaluation is key to assessing whether the current situation is acceptable for the patient, or whether there is an indication for follow-up therapy.

***Back to the case study***

Our patient had a COPD GOLD IV/D with severe hyperinflation, total respiratory insufficiency, frequent exacerbations, poor exercise tolerance, severe cachexia and an anxiety disorder. Available treatment options for our patient were discussed in our multidimensional respiratory failure meeting. It was clear that she needed a multidimensional approach to achieve her goal (improving HRQoL).

Because of her frequent exacerbations, the addition of azithromycin maintenance therapy was suggested. Furthermore, reducing benzodiazepines was discussed, but the patient had serious doubts about this because of anxiety and psychiatric decompensating in the past. Because of her severe hyperinflation, BLVR was discussed. However, the high exacerbation rate combined with bronchopathy on the HRCT scan made the patient ineligible for this kind of treatment at this time point. Because of the hypercapnia and complaints of morning headaches and bad sleep, the patient was thought to be a good candidate for long-term NIV, although her anxiety could be a limiting factor. Lung transplantation was discussed, and although she was not formally rejected, perioperative risks were estimated to be high

because of her low body mass index. We discussed with the patient that combining NIV in a multidisciplinary rehabilitation program, focusing on improving exercise tolerance, reducing anxiety, improving breathing techniques and gaining muscle mass, would be most suitable at this time. She was initiated on NIV prior to the pulmonary rehabilitation in our rehab center, which she tolerated well, although she needed time and support to get used to the ventilator. Eventually, she finished this trajectory with good result.

After 2 years of home NIV, with good compliance and a reduction in exacerbation frequency, she was again discussed in our multidisciplinary meeting. Her main complaint was severe dyspnea on minimal exertion. An HRCT scan now showed that her bronchopathy was only minimal, and her exacerbation frequency had decreased to just once a year with azithromycin maintenance therapy. Her $FEV_1$ was stable and the RV/TLC ratio was now 73%. She still tried to go to her physiotherapist for training two times a week. We decided to evaluate her again for BLVR, and she was referred for lung transplantation.

Quantitative CT-analysis was performed, which revealed a destruction score of 35% at −950 HU of the left lower lobe, compared to 28% of the right lower lobe, and both the right and left major fissure were 100% complete. Therefore, she was scheduled for a bronchoscopy with placement of endobronchial valves of the right lower lobe after Chartis assessment, which revealed no collateral ventilation. She obtained good and persistent results from the bronchoscopic treatment, and at 65 years of age, she finally decided to renounce lung transplantation.

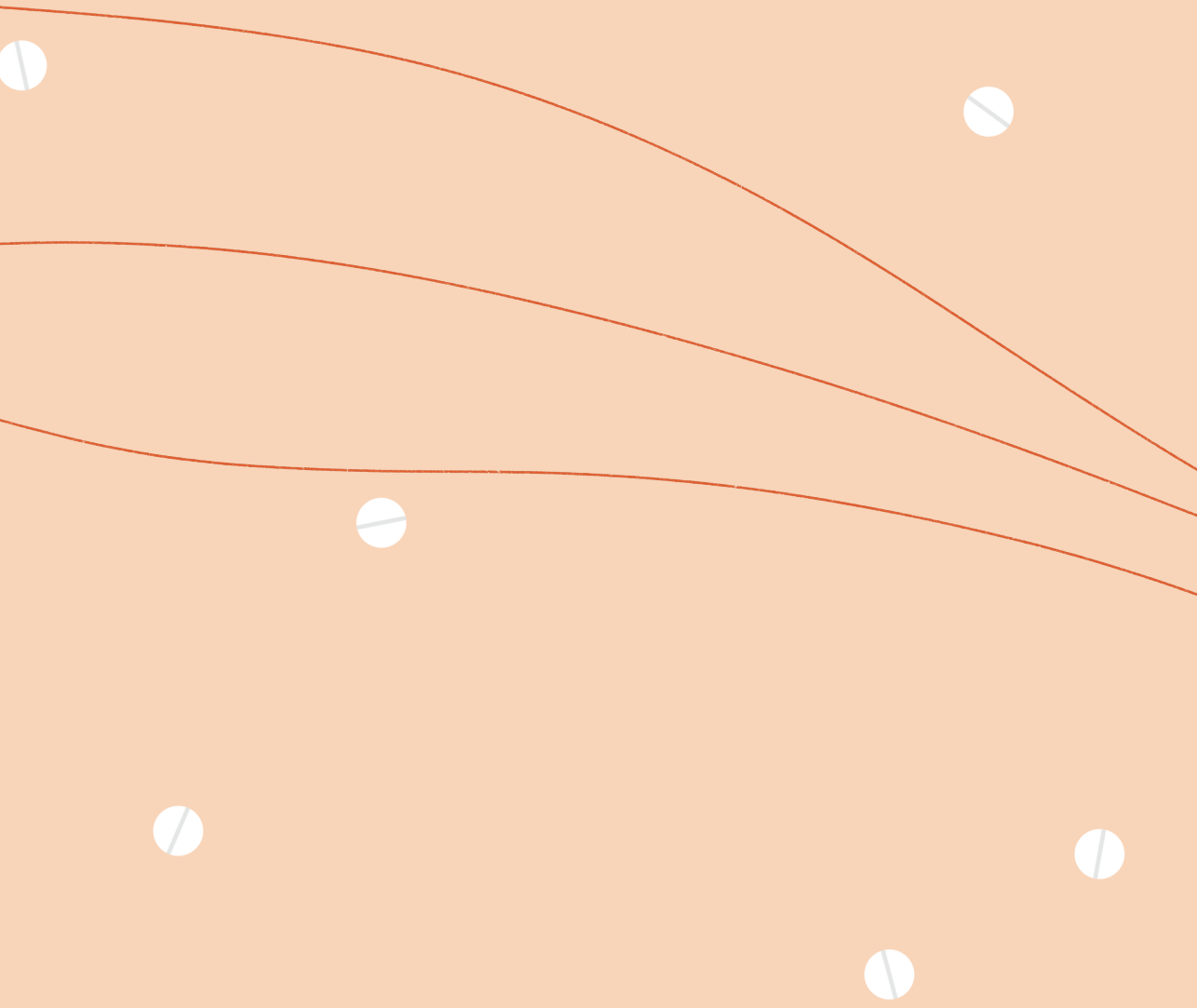
**Table 2** | Overview of the treatable traits in severe COPD and the treatment options that can be offered

| Treatable trait | Treatment | Suitable patients | Effect | Quality of evidence [110] |
|---|---|---|---|---|
| **Hyperinflation** | Endobronchial Valves | Severe hyperinflation (RV > 175% predicted or RV/ TLC ≥0.58) Absence of collateral ventilation / complete fissures No frequent exacerbations | + | High |
| | Endobronchial Coils | Severe hyperinflation (RV > 200% predicted or RV/ TLC ≥0.58) No frequent exacerbations No significant bronchopathy | + | High |
| | Lung volume reduction surgery | Heterogeneous upper lobe predominant emphysema | + | High |
| | Bronchoscopic thermal vapor ablation | Heterogeneous upper lobe predominant emphysema | + | Moderate |
| **Chronic Respiratory Failure** | LTOT | Daytime $PaO_2$ < 7.2 kPa (or $PaO_2$ < 8.0 kPa with signs of right heart failure) | + | Moderate |
| | Chronic NIV | Daytime $PaCO_2$ ≥ 6 kPa and complaints of hypoventilation | + | Moderate |
| | nHFT | unknown | + | Low |
| **Frequent Exacerbators** | Inhaled corticosteroids | Patients with ≥ 2 exacerbations/year (and blood eosinophilia) | + | High |
| | Oral corticosteroids | Patients with frequent exacerbations | - | Very Low |
| | Roflumilast | Patients with ≥ 2 exacerbations/year, chronic bronchitis, $FEV_1$ < 50%pred | + | Moderate |
| | Macrolides | Patients with ≥ 2 exacerbations/year | + | High |
| | PR | All patients | + | High |
| | NIV | Patients with a persistent severe hypercapnia ($PaCO_2$>7.2 kPa) 2-4 weeks after an exacerbation | + | Moderate |
| | nHFT | To be determined | + | Low |
| | TLD* | To be determined | + | Low |

**Table 2** | *Continued*

| Treatable trait | Treatment | Suitable patients | Effect | Quality of evidence [110] |
|---|---|---|---|---|
| **Pulmonary Hypertension** | LTOT | Daytime $PaO_2$ < 7.2 kPa (or $PaO_2$ < 8.0 kPa with signs of right heart failure) | + | Moderate |
| | PAH med | Unknown | - | Low |
| | Chronic NIV | Chronic Respiratory Failure | + | Low |
| | BLVR | Patients with severe hyperinflation | + | Low |
| **Extrapulmonary treatable traits** | PR | All patients with persistent respiratory symptoms, exercise intolerance, low muscle strength and/or psychological symptoms | + | High |
| | Nutritional support | BMI < 21<br>BMI > 27 | + | High<br>Low |
| **Severe disability despite treatment** | Breathlessness service<br>Low-dose opioids<br>Handheld fan | Patients with refractory breathlessness | +<br>+<br>+ | Low<br>Low<br>Low |
| | ACP | All patients! | + | Low |
| | Lung Transplantation | Patients with limited comorbidities and an expected survival < 2 years | + | Moderate (large effect, no RCTs) |

*$FEV_1$: forced expiratory volume in 1 s; $PaCO_2$ : arterial carbon dioxide tension; RV: residual volume; TLC: total lung capacity; $PaO_2$ : arterial oxygen tension; PAH: pulmonary arterial hypertension; BMI: body mass index; REM: rapid eye movements; RCTs: randomised controlled trials; LTOT: long-term oxygen therapy; NIV: non-invasive ventilation; nHFT: nasal high-flow therapy; PR: pulmonary rehabilitation; TLD: targeted lung denervation; BLVR: bronchoscopic lung volume reduction; ACP: advance care planning. *: Only in research setting; the level of the evidence was assessed with the GRADE system [159].*



CHAPTER 3

# The effects of lung volume reduction treatment on diffusing capacity and gas exchange

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## Abstract

Lung volume reduction (LVR) treatment in patients with severe emphysema has been shown to have a positive effect on hyperinflation, expiratory flow, exercise capacity and quality of life. However, the effects on diffusing capacity of the lungs and gas exchange are less clear. In this review, the possible mechanisms by which LVR treatment can affect diffusing capacity of the lung for carbon monoxide ($DL_{CO}$) and arterial gas parameters are discussed, the use of $DL_{CO}$ in LVR treatment is evaluated and other diagnostic techniques reflecting diffusing capacity and regional ventilation (*V'*)/perfusion (*Q'*) mismatch are considered. A systematic review of the literature was performed for studies reporting on $DL_{CO}$ and arterial blood gas parameters before and after LVR surgery or endoscopic LVR with endobronchial valves (EBV). $DL_{CO}$ after these LVR treatments improved (40 studies, n=1855) and the mean absolute change from baseline in %predicted $DL_{CO}$ was +5.7% (range −4.6% to +29%), with no real change in blood gas parameters. Improvement in *V'*inhomogeneity and *V'/Q'* mismatch are plausible explanations for the improvement in $DL_{CO}$ after LVR treatment.


3

## Introduction

Lung volume reduction (LVR) surgery in patients with diffuse emphysema was first described as early as 1957 by BRANTIGAN *et al.* [27]. Although this treatment gave significant clinical improvement in three quarters of treated patients, the high mortality rate prevented this surgical technique from becoming a regularly used treatment option for many decades. In the 1990s there was a revival of LVR surgery, which started with the reports of COOPER and colleagues [28, 29] who performed bilateral partial lung resection and documented improvement in lung function and symptoms with a mortality rate of 4%. In 2003 the large multicenter National Emphysema Treatment Trial (NETT) demonstrated improvement in lung function, dyspnea, exercise capacity and survival with LVR surgery compared to medical treatment, mainly in the subset of patients with upper lobe dominant emphysema and low baseline exercise capacity [30]. A high risk subgroup of patients was identified with baseline % predicted forced expiratory volume in 1 s ($FEV_1$) of ≤20%, combined with either a homogeneous distribution of emphysema or % predicted diffusing capacity of the lung for carbon monoxide ($DL_{CO}$) <20% [30]. Important post-operative complications of LVR surgery are prolonged air leak, pneumonia, prolonged mechanical ventilation and reoperation [28, 29].

The substantial morbidity and mortality accompanying LVR surgery elicited interest in developing less invasive endobronchial techniques for lung volume reduction. In 2002, TOMA *et al.* [160] reported the first pilot study in which endobronchial valves (EBVs) are placed endoscopically in patients with severe emphysema. Results were promising and in recent years multiple randomized clinical trials have been published in which EBV placement shows statistically significant and clinically relevant effects on lung function, exercise capacity and quality of life [32-35, 65, 80]. In the current Global Initiative for Chronic

Obstructive Lung Disease (GOLD) guidelines, EBV placement is recognized as an additional treatment option in a specific group of patients having emphysema, hyperinflation and proven absence of collateral ventilation [1].

The main effect of LVR treatment is thought to be improved lung compliance due to better matching of the size of the lungs to the size of the thorax containing them. This in turn results in improved lung elastic recoil at similar thoracic inspiratory volume, better expiratory airflow and reduced dynamic and static hyperinflation [25]. Indeed, the effects of LVR treatment on $FEV_1$, vital capacity (VC), total lung capacity (TLC) and residual volume (RV) are well established. However, much less is known about the effect of LVR treatment on the diffusing capacity of the lungs and on gas exchange. In this review, we summarize results from studies reporting the effects of LVR surgery and endoscopic LVR with EBVs on $DL_{CO}$ and gas exchange parameters. Furthermore, we propose mechanisms by which LVR treatment can affect both $DL_{CO}$ and gas exchange, and discuss the use of $DL_{CO}$ measurement in selecting patients for LVR treatments. Finally, we consider the suitability of alternative techniques for measuring diffusing capacity and regional ventilation ($V'$)/perfusion ($Q'$) mismatch in selecting patients with emphysema for LVR treatment.



### *Diffusing capacity of the lung for carbon monoxide*

The method to measure lung diffusion through carbon monoxide uptake during a single breath was developed by KROGH *et al*. over 100 years ago [161]. In 1957, this method was modified by OGILVIE *et al*. [162] to measure the pulmonary diffusing capacity for carbon monoxide. This method, using modernized rapid gas analysis, remains the most common standard for measurement of lung diffusion throughout the world [163]. The patient is asked to exhale maximally and then slowly inspire to TLC and perform a 10 s breath-hold maneuver. During inspiration, the patient inhales a test gas which contains a known low concentration of carbon monoxide (approximately 0.03%) and an inert tracer gas (*e.g.* helium). By measuring the concentration of the exhaled carbon monoxide and tracer gas the $DL_{CO}$ can be calculated. The concentration difference in carbon monoxide is used to calculate a rate constant for alveolar–capillary carbon monoxide transfer, the transfer coefficient of the lung for carbon monoxide ($K_{CO}$). The concentration difference in the tracer gas represents the dilutional effect used to calculate the alveolar volume ($V_A$) [163].

### *Diffusing capacity in patients with emphysema*

In 1977, WAGNER *et al*. [7] showed by extensive testing with multiple inert gasses that emphysema is associated with a significant high regional $V'/Q'$ ratio. They attributed the degree of hypoxemia in their group to $V'/Q'$ mismatch and shunting, leading to the conclusion that diffusing impairment plays no role in hypoxemia in resting patients with emphysema. As there was no imaging available in this study, it cannot be concluded that this pattern is represented throughout the heterogeneous spectrum of patterns and severity of lung parenchymal emphysema and airway involvement. In fact, emphysema is associated with

an impaired $DL_{CO}$ and a clear inverse linear relationship has been demonstrated between $DL_{CO}$ and the severity of emphysema on computed tomography (CT) [164]. Furthermore, in chronic obstructive pulmonary disease (COPD) there is an association between $DL_{CO}$ and mortality [165], and decreased $DL_{CO}$ is associated with an increased likelihood of reduced arterial oxygen tension ($PaO_2$) during rest and with exertion [166, 167]. The reason $DL_{CO}$ is impaired in patients with emphysema is thought to be due to the loss of gas exchange surface. Pulmonary microvascular blood flow has been shown to be reduced in mild to severe COPD and is related to emphysema severity on the chest CT scan [6, 168]. Pathophysiologically, the reduced quantity of gas exchange surface can be interpreted as a diffusing impairment. However, it can also be interpreted as a *V′/Q′* mismatch where there is reduced capillary blood volume in areas of largely preserved *V′* (*i.e.* high *V′/Q′* ratio). Reality is probably more complex than this however, as *V′* is also affected in COPD. For example, air trapping or airflow obstruction can result from bronchitis, small airways disease or emphysema [4]. *V′/Q′* disturbances have been shown to be common even in the early stages of COPD [169]. Furthermore, regional heterogeneity is likely to result in hyperinflated regions impacting *V′* or *Q′* in adjacent lung regions. The reliability of $DL_{CO}$ testing in emphysema, in order to estimate the anatomical loss of gas exchange area, can be affected in several ways (figure 1). First, inhomogeneous *V′* may be present due to the presence of both airways disease and/or emphysema [170, 171]. THOMPSON *et al.* [171] developed mathematical models in which they tested different types of inhomogeneous *V′*. When there was inhomogeneity of inspired volume or end-expiratory volume, $DL_{CO}$ was underestimated. In contrast, inhomogeneity of alveolar compartment size led to an overestimation of $DL_{CO}$. In the lungs of a patient with COPD, these types of inhomogeneous *V′* can co-exist, which makes it difficult to predict the combined effect of these errors on measured $DL_{CO}$. Methodological issues in COPD patients can affect the reliability of the measurements. For example, patients with COPD can have difficulty with the 10 s breath-hold maneuver. In contrast to healthy subjects, a shorter breath-holding time decreases $DL_{CO}$ in patients with airflow obstruction and emphysema [172]. On the other hand, the reduced expiratory flow rate in patients with COPD may lead to an overestimation of $DL_{CO}$ [173]. The $V_A$/TLC ratio can help to identify the maldistribution of inspired gas and poor mixing of gases in the lung. Normally the $V_A$/TLC ratio exceeds 0.85, however, in patients with COPD this ratio is often much lower, indicating that $DL_{CO}$ measurement might be influenced by inhomogeneous *V′*, such that potentially functional lung units are not involved in gas distribution [174, 175].

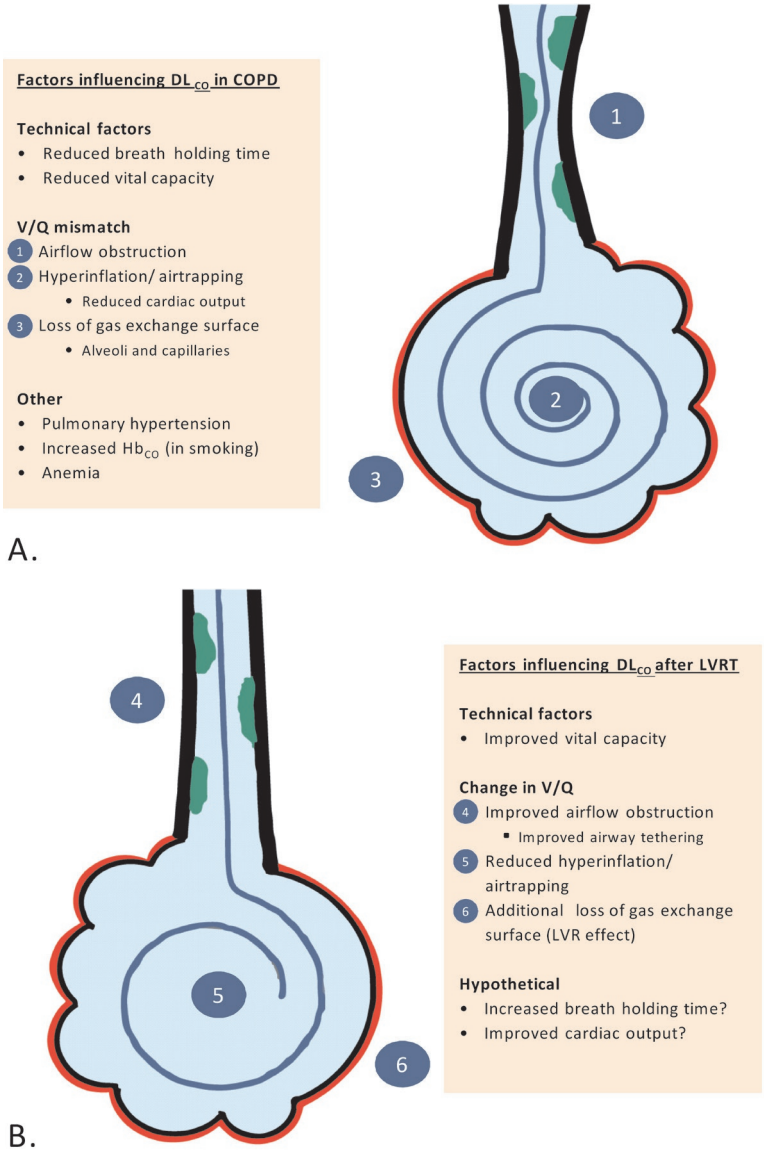


*Figure 1: a) Factors influencing the measurement of diffusing capacity of the lung for carbon monoxide ($DL_{CO}$) in patients with COPD. b) Factors influencing $DL_{CO}$ after lung volume reduction treatment. VC: Vital Capacity; V'/Q': ventilation/perfusion ratio; CO: cardiac output; PH: pulmonary hypertension; $Hb_{CO}$: carboxyhemoglobin.*

### *Reported effect of lung volume reduction surgery and endoscopic lung volume reduction on $DL_{CO}$ and gas exchange*

We performed a literature search for studies which investigated either LVR surgery or endoscopic LVR with EBVs; specifically studies that reported on $DL_{CO}$, alveolar–arterial oxygen tension difference ($P(A\text{-}a)O_2$; alveolar–arterial oxygen gradient), arterial carbon dioxide tension ($PaCO_2$) and $PaO_2$ before and after LVR treatment. Since *V′* inhomogeneity is common in COPD and can lead to an overestimation of $K_{CO}$ [176], we excluded this parameter from our search strategy (see supplementary material). Information on baseline and follow-up values for % predicted $DL_{CO}$ was given in 41 studies, 26 studies regarding LVR surgery (figure 2a, supplementary table S1) and 15 studies with EBVs (figure 2b, supplementary table S2). In five studies, $DL_{CO}$ values where only given in absolute values (supplementary table S3). In all but four studies there was a mean increase in $DL_{CO}$ after treatment, which was statistically significant in 19 studies. The weighted mean increase in % predicted $DL_{CO}$ was 5.7% (range −4.6% to 29%). The suggested minimal clinically important difference (MCID) for $DL_{CO}$ is a relative increase in % predicted $DL_{CO}$ of 11% [177]. The weighted relative increase in % predicted $DL_{CO}$ was 18.4%, with 24 out of 40 studies reporting an increase larger than 11%.

Ten studies that reported on a standard deviation, range or interquartile range for change in $DL_{CO}$ showed a very broad distribution (supplementary table S4). This implies that even though there may be a (small) positive change in $DL_{CO}$ after LVR treatment on average, the effects on an individual level can be variable, ranging from a negative effect to a large positive effect. Unfortunately, due to the various ways in which the data was reported, it could not be calculated whether this increase was statistically significant.

In 35 studies, information was given on $PaO_2$ and $PaCO_2$ before and after treatment (table 1). There was a weighted mean improvement in $PaO_2$ of +0.64 kPa (range −0.40 kPa to +1.30 kPa) and a weighted mean decrease in $PaCO_2$ of −0.31 kPa (range −0.90 kPa to +0.60 kPa). A total of 36 studies were found in which the $P(A\text{-}a)O_2$ gradient was either reported or where it was possible to calculate it from values given for $PaO_2$ and $PaCO_2$ before and after treatment (table 1, supplementary table S5). The following formula was used to calculate the $P(A\text{-}a)O_2$ gradient: $((FIO_2)\cdot(\text{atmospheric pressure-}H_2O\text{ pressure})-(PaCO_2/0.8))-PaO_2$ (where inspiratory oxygen fraction ($FIO_2$) was assumed to be 21% (room air), atmospheric pressure was assumed to be 101.33 kPa and $H_2O$ pressure was assumed to be 6.3 kPa) [178]. The weighted mean change in $P(A\text{-}a)O_2$ gradient after treatment was −0.18 kPa (range −1.10 kPa to 1.60 kPa). Statistical significance is unknown for these values; however, the wide range shows that there is great variation in response to LVR treatment for $P(A\text{-}a)O_2$ gradient. Fifteen studies reported on % predicted $DL_{CO}$ and $PaO_2$ combined with $PaCO_2$ (supplementary table S6). While all but one study showed a positive effect on $DL_{CO}$, the $P(A\text{-}a)O_2$ gradient was stable or increased in four studies. There was no significant correlation between change in $DL_{CO}$ and $P(A\text{-}a)O_2$ gradient.

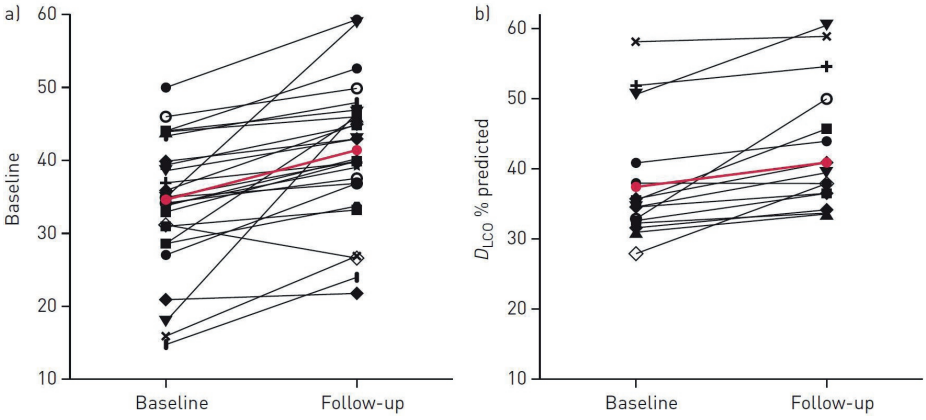


*Figure 2 a) Change in % predicted diffusing capacity of the lung for carbon monoxide ($DL_{CO}$) from before to after lung volume reduction surgery, as reported in 25 studies. b) Change in % predicted $DL_{CO}$ from before to after endoscopic lung volume reduction with endobronchial valves, as reported in 15 studies. Weighted mean change is represented in the red line.*

**Table 1** | Change in diffusing capacity and gas exchange parameters after lung volume reduction treatment.

| Parameter | No. of studies | No. of patients | Before LVR | After LVR | Difference |
|---|---|---|---|---|---|
| **$DL_{CO}$ (%pred)** | 41 | 1864 | 35.6 | 41.3 | +5.7 |
| **$PaO_2$ (kPa)** | 35 | 1375 | 8.72 | 9.36 | +0.64 |
| **$PaCO_2$ (kPa)** | 35 | 1375 | 5.53 | 5.22 | -0.31 |
| **p(A-a)$O_2$ gradient (kPa)** | 36 | 1408 | 4.23 | 4.05 | -0.18 |

*$DL_{CO}$= diffusing capacity, $PaO_2$ = arterial oxygen tension, $PaCO_2$ = arterial carbon dioxide tension, p(A-a)$O_2$ gradient = Alveolar-arterial oxygen gradient.*

### *Potential mechanisms by which LVR surgery and endoscopic LVR can influence gas exchange and $DL_{CO}$ testing*

As shown in figure 1, the measurement of $DL_{CO}$ in COPD patients can be influenced by several mechanisms, such as reduction in gas exchange surface, an altered *V′/Q′* ratio, *V′* inhomogeneity (*e.g.* air trapping) and pulmonary hypertension (PH). The same mechanisms can also influence gas exchange.

When LVR treatment is performed, these mechanisms may change and can therefore alter the outcome of $DL_{CO}$ measurement as well as functional gas exchange. The ultimate effect on diffusing capacity and gas exchange is likely related to the balance of these mechanisms. Due to patient and treatment heterogeneity, the net result of LVR treatment may vary greatly, as has been shown above in the results section. The impact of LVR treatment on $DL_{CO}$ was investigated in an animal model where LVR surgery was performed on rabbits with emphysema. Resecting more than 30% of total lung tissue led to a decrease in $DL_{CO}$;

however, there was still a positive effect on spirometry and RV [179]. This suggests that the volume of lung tissue which can be resected or blocked by EBVs can be an important limiting factor. In another study, in 14 patients undergoing LVR surgery, changes in gas exchange were investigated with the multiple inert-gas elimination technique. In this study, change in $PaO_2$ was found to be explained mostly by improved *V′/Q′* inequality, whereas changes in $PaCO_2$ were related to variables concerning static hyperinflation and airflow potential [180].



The following questions may be useful when thinking about the effects of LVR surgery and endoscopic LVR on $DL_{CO}$ and gas exchange:

1. What was the regional *V′–Q′* distribution in the lung section(s) that have been surgically removed or blocked by EBVs and in the remaining lung sections?
2. In what way does overall *V′* change after LVR treatment?
3. In what way does overall lung *Q′* change after LVR treatment?
4. Was there compression of the removed or blocked lung tissue on the remaining lung sections?
5. Are there differences between LVR surgery and endoscopic LVR with EBVs influencing the treatment effect?

*Question 1:*
***What was the regional V'-Q' distribution in the lung section(s) that have been surgically removed or blocked by EBVs, and in the remaining lung sections?***

With respect to *V′–Q′* distribution in LVR treatment, ALBERT *et al.* [181] suggested four different scenarios in LVR surgery, with different outcomes on gas exchange. If an area with a high *V′/Q′* ratio is resected, more *V′* could go to the remaining lung sections. If there is already a high *V′/Q′* ratio in these lung sections, the overall effect will be an even worse *V′/Q′* distribution. However, if there is a low *V′/Q′* ratio before treatment, an increase in *V′* would lead to a better *V′/Q′* distribution and improvement of gas exchange. When resecting an area with a low *V′/Q′* ratio, more blood flow will go to the remaining lung sections. If the remaining lung sections have a high *V′/Q′* ratio this can lead to a better *V′/Q′* distribution. Conversely, an increase in blood flow in lung sections with an already low *V′/Q′* ratio leads to a worse *V′/Q′* distribution. Patients who are selected for LVR are typically patients with severe emphysema. As mentioned earlier, these patients are shown to have considerable regions of high *V′/Q′* ratio [7]. As such, the most likely scenario is probably the removal or blockage of areas with a high *V′/Q′* ratio, because in general areas with severe emphysema are treated. The effect this has on gas exchange depends on the regional *V′/Q′* mismatch in the remaining lung sections. The best results for $PaO_2$ can be expected when the remaining lung sections have low *V′/Q′* distribution, which is more likely to be present in heterogeneous emphysema. However, it is important to note that in the above mentioned scenarios it is assumed that respiratory minute ventilation and cardiac output (CO) are unchanged by LVR surgery.

*Question 2:*
*In what way does overall V' change after LVR treatment?*

Several studies [182-185] have analyzed the effect of LVR surgery on respiratory minute volume and alveolar ventilation, including two studies by the group of Albert [182, 185]. All these studies show an increase in respiratory volume and tidal volume during exercise, as well as a decrease in breathing frequency, although no such changes are reported at rest. In our analysis, we found that there was an increase in $PaO_2$ and a decrease in $PaCO_2$ in five studies [181, 186-189], while the $P(A\text{-}a)O_2$ gradient remained stable at rest or increased. This suggests that respiratory minute volume at rest can indeed increase after LVR treatment.



*Question 3:*
*In what way does overall lung Q' change after LVR treatment?*

Reports on change in CO after LVR surgery have shown mixed effects [190, 191]. When LVR surgery started to become a treatment for patients with severe emphysema, one of the main concerns was development of postoperative PH and, consequently, reduced cardiac function due to reduction of the pulmonary vascular bed. One prospective study did show an increase in pulmonary artery systolic pressure, but this was not accompanied by a reduction in cardiac function [192]. Other studies showed no change in mean pulmonary pressure [190, 191]. Furthermore, improvement in right-ventricular function after LVR surgery was demonstrated in a prospective trial [187]. The varying responses of pulmonary hemodynamics to LVR surgery demonstrate the heterogeneity of both patient-related factors and surgical treatment effects. An inverse relation between static hyperinflation and heart size has been established in patients with COPD [193]. More severe hyperinflation was associated with a smaller heart size, which in turn was associated with impaired left-ventricular diastolic filling and impaired right-ventricular function [193]. Recently, a study was published where treatment with a long-acting $\beta_2$-agonist–long-acting muscarinic antagonist combination resulted in an increase in cardiac index in patients with COPD and hyperinflation [194]. As such, CO may hypothetically increase if LVR treatment successfully diminishes static hyperinflation. However, this has not consistently been demonstrated in clinical trials so far, probably due to individual patient variation and differences in intervention techniques.

*Question 4:*
*Was there compression of the removed or blocked lung tissue on the remaining lung sections?*

Whether there is compression on the surrounding lung tissue by the treated lung tissue is more difficult to assess in a research setting. However, when assessing a chest CT scan of a patient with severe emphysema in clinical practice, compression of lung tissue by a hyperinflated lobe is sometimes clear to see. When treating this hyperinflated lobe, either endobronchially or surgically, the compressed lung tissue will exhibit improved *V'*, which is likely to have a positive effect on gas exchange. The extent of this effect will depend on the amount and functional quality of the compressed lung tissue.

*Question 5:*
*Are there differences between LVR surgery and endoscopic LVR with endobronchial valves influencing the treatment effect?*

It seems likely that LVR surgery and endoscopic LVR with EBVs have largely the same average effects on $DL_{CO}$ and gas exchange, and also exhibit similar individual patient variations in response; however, there are also important differences. First, the lung tissue (including blood vessels) is completely removed following surgery. Whereas, in successful endoscopic LVR, there is an atelectasis of the lung lobe where there may still be some remaining blood flow present. When atelectasis of the left lung was induced in healthy dogs, a significant reduction in the percentage of the total blood flow was measured in the atelectatic lung. The maximum reduction, from 43% to 12% of total blood flow, was measured after 60 min and remained unchanged for the total of 4 h that the atelectasis existed [195]. A more recent study in human emphysema used lung scintigraphy to assess $V'$ and $Q'$ over both the target lobe and untreated lobes before and 8 weeks after EBV placement [196]. This study showed a mean 43% reduction of $Q'$ in the target lobe, with significant increases in $Q'$ at the contralateral side. It should be noted that it is difficult to assess the reduction in blood flow in the target lobe very precisely with this technique. As such, some shunting probably remains in the atelectatic target lobe, but the precise amount of shunting and its clinical relevance are not known.

Surgical lobectomies for LVR are also presently performed; however, in the majority of published trials surgery is mainly performed bilaterally [27-30], whereas endoscopic LVR with EBVs is performed unilaterally [32-35, 65]. Furthermore, lung tissue resection is not confined to anatomical borders, so the surgeon can resect the most emphysematous tissue on both sides. Endoscopic LVR with EBVs is confined to one or at most two lobes when the middle lobe is involved. Less emphysematous lung tissue within the target lobe will be collapsed as well, which could have a less optimal effect on gas exchange and $DL_{CO}$.

### *The use of $DL_{CO}$ testing to select patients for LVR treatment*

Currently, it is common practice not to treat patients with very low $DL_{CO}$ given the high risk of death as identified in the NETT [30]. This is in line with the higher mortality rates generally observed in COPD patients with low $DL_{CO}$ [165]. However, excluding some patients with very low $DL_{CO}$ may lead to the exclusion of patients who may actually benefit from LVR treatment. Two retrospective analyses [197, 198] have shown no increased mortality and a positive effect on $FEV_1$, RV and $DL_{CO}$ after LVR surgery in patients fulfilling the NETT high risk criteria. Therefore, using $DL_{CO}$ as a measurement to select patients for LVR treatment appears to have its limitations.

The general assumption is that $DL_{CO}$ reflects the quality and quantity of the alveolar–capillary gas-exchange surface. Therefore, in the light of LVR (where we sacrifice part of the gas-exchange area in favor of mechanical advantages) it seems rational to use $DL_{CO}$ testing for risk assessment (*i.e.* is there enough gas-exchange surface left to sacrifice a

part of it?). An arbitrary cut-off point (such as % predicted $DL_{CO}$ <20%) could then indicate the tipping point where the risk for respiratory failure becomes too large. This assumption would be supported by a clear reduction in $DL_{CO}$ after LVR treatment. However, with our meta-analysis we have demonstrated that $DL_{CO}$ frequently improves after LVR treatment. As such, the assumption that $DL_{CO}$ reflects alveolar gas-exchange capability is apparently not (completely) valid, at least in severe emphysema patients. Improved $V'$ and $Q'$ of the adjacent and other lung lobe(s) are probably responsible for the observed improvements in $DL_{CO}$ after successful LVR treatment. Consequently, we should use the $DL_{CO}$ test not only as a tool to assess risk but also as a tool to assess potential benefit, which requires a switch in thinking. The question then arises as to how $DL_{CO}$ should be used to discriminate between patients who might benefit from LVR treatment and patients who are at risk for developing respiratory failure after treatment. The answer is probably that $DL_{CO}$ as a single measurement at baseline is too unreliable. Using $DL_{CO}$ in combination with other variables, such as $FEV_1$, arterial blood gas analysis and distribution of lung emphysema seems attractive. However, at this moment in time we do not have validated algorithms that may support individual decision making. We speculate that low $FEV_1$ easily associates with false low $DL_{CO}$ measurements and as such excluding subjects solely on the basis of low $FEV_1$ and low $DL_{CO}$ is not recommended. Low $DL_{CO}$ in combination with low $PaO_2$ seems unattractive for LVR treatment unless a patient has significant heterogeneous emphysema, in which case we believe LVR can still be considered because a low $V'/Q'$ ratio in an adjacent lobe can be improved on treatment. If patients have low $DL_{CO}$, high $PaCO_2$ and homogeneous emphysema, we believe LVR is less attractive because a high $V'/Q'$ ratio in an adjacent lobe can deteriorate (see question 1 above). To summarize, we recommend the use of $DL_{CO}$ not only as a tool to assess risk for respiratory failure but also as a tool to assess potential benefit from LVR treatment. However, as individual decision making is still difficult for many emphysema patients with low $DL_{CO}$, we clearly need additional diagnostic tools that investigate other aspects of gas exchange.

***Are there better diagnostic tests to select patients?***

Diagnostic tests which can accurately reflect the total quantity of gas-exchange surface and/or regional $V'/Q'$ ratios in the lung would be helpful in assessing the probability of a successful LVR treatment (*i.e.* one which results in a reduction of hyperinflation while preserving or even improving gas exchange).

*Diffusing capacity of the lung (gas-exchange surface)*

As measuring $DL_{CO}$ by the single-breath method ($DL_{CO}$ SB) can be technically difficult in COPD patients and the outcome $DL_{CO}$ measurement is influenced by $V'$ inhomogeneity, we assessed whether there are better techniques to reflect diffusing capacity of the lung in these patients. First, the use of a real-time gas-analyzer system, in which both the concentration of tracer gas and that of carbon monoxide are measured continuously, has been shown to provide a better estimate of $V_A$ [163], which is notoriously difficult in patients

with COPD [175]. Techniques that are rarely used include the so-called "rebreathing" method and the "open-circuit" method. As with $DL_{CO}$ SB, both were found to be influenced by *V′* inhomogeneity [171]. Three-equation $DL_{CO}$ is a variant of the single-breath method where three equations are used, one for each part of the single-breath manoeuvre (inhalation, breath-holding and exhalation) [199]. In healthy persons, three-equation $DL_{CO}$ remained constant despite variations in duration of breath-holding and expiration [199]. Unfortunately, a shorter breath-holding time did result in lower $DL_{CO}$ in patients with emphysema, which the authors related to *V′* maldistribution [172]. Nitric oxide can be used instead of carbon monoxide, thus measuring the diffusing capacity of the lung for nitric oxide ($D_{LNO}$). Nitric oxide can bind approximately 1500 times faster to hemoglobin (Hb) than carbon monoxide and is therefore proposed to be a better representative of the diffusive properties of the alveolar–capillary membrane than $DL_{CO}$ [200]. There may be some general advantages of $D_{LNO}$ over $DL_{CO}$, for example, $D_{LNO}$ is unaffected by carboxyhemoglobin ($Hb_{CO}$), only minimally affected by Hb, and relatively unaffected by $FiO_2$ and ambient pressure [200]. One study investigating heavy smokers showed that the transfer coefficient of the lung for nitric oxide ($K_{NO}$) was slightly more sensitive than $K_{CO}$ for detecting emphysema [201]. Furthermore, the $D_{LNO}/DL_{CO}$ ratio was increased in patients with emphysema; however, no difference between $DL_{CO}$ and $D_{LNO}$ was found in the same study [201]. As such, even though there are various techniques for measuring the diffusing capacity of the lungs, in general these techniques have the same shortcomings as $DL_{CO}$ SB.

*Assessing regional V′/Q′ ratio*

Two-dimensional *V′/Q′* scintigraphy is an insufficient technique for accurately mapping regional *V′/Q′* ratios. However, there are several more advanced imaging techniques which could potentially be used for this purpose. Single-photon emission CT ventilation/perfusion (VQ SPECT) is a technique where three-dimensional *V′/Q′* images can be related to CT images [202]. With this technique the percentage of total lung volume, *Q′* and *V′* can be quantified for each lung lobe [203]. Advanced CT scanning, for example four-dimensional CT and multiple-detector CT, can generate functional maps of *V′* and *Q′* [204, 205]. Magnetic resonance imaging can also be used for mapping of *V′* and *Q′*, for example by using hyperpolarized xenon (129Xe) as a tracer gas or via free-breathing Fourier-decomposition MRI [205]. In conclusion, there are several imaging techniques with which regional *V′/Q′* can be mapped; however, it is important to note that these techniques are costly and not readily available everywhere. Furthermore, the relatively high radiation dose for four-dimensional CT scanning should be taken into account.

*Summary and future research questions*

On average, LVR surgery and endoscopic LVR with EBVs lead to a small improvement in $DL_{CO}$ in patients with severe emphysema and hyperinflation, even though there is a reduction in gas-exchange surface. However, there is a great variation in the response on an individual level, probably related to both patient and treatment heterogeneity. We propose that the reason for improved $DL_{CO}$ is improvement in the *V′/Q′* ratio and in *V′* inhomogeneity in the

regionally expanded non-targeted lung. $DL_{CO}$ is commonly used in screening patients for LVR treatment and may have some value in predicting the eligibility of a patient with severe emphysema for LVR treatment. However, there are several limitations and uncertainties in using this measurement in patients with severe emphysema. Therefore, we recommend measuring $DL_{CO}$ before LVR treatment, but only in combination with other diagnostic measurements such as arterial blood gas analysis, quantitative CT-analysis of emphysema destruction and *Q'* scintigraphy. Other diagnostic methods to assess the quantity of gas-exchange surface and regional *V'/Q'* ratios would be helpful, but are currently not readily available. Therefore, further research is needed to obtain more clarity.



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## Supplementary material

### Search Strategy

We performed a search for studies concerning lung volume reduction surgery and bronchoscopic lung volume reduction with endobronchial valves. If information on $DL_{CO}$, p(A-a)$O_2$ gradient, $PaO_2$ combined with $PaCO_2$ before and after treatment was given, the article was included in the analysis



Suitablity of the articles was screened by title and abstract. Clinical trials, observational studies and retrospective analyses were included. Other selection criteria were full text availability and text published in the English language.

The following search terms were used for bronchoscopic lung volume reduction with endobronchial valves: ‘Endobronchial Valves’; ‘Endobronchial Valve’; ‘Lung Volume Reduction Valve’; Bronchial Valve’.

For studies concerning LVRS the search term ‘Lung Volume Reduction Surgery’ in title or abstract was used.

**Table S1** | $DL_{CO}$ before and after Lung Volume Reduction Surgery

| Study | Year | N (treated) | Interval (months) | Baseline $DL_{CO}$ (%pred) | Follow Up $DL_{CO}$ (%pred) | $\Delta DL_{CO}$ (%absolute) | P-value |
|---|---|---|---|---|---|---|---|
| **Sciurba** [187] | 1996 | 20 | 3 | 44 | 47 | 3 | 0.15 |
| **Brenner** [206] | 1997 | 145 | Unknown | 28.5 | 46.1 | 17.6 | <0.001 |
| **Martinez** [52] | 1997 | 17 | 3 to 6 | 43.3 | 48.2 | 4.9 | 0.13 |
| **Gelb** [207] | 1998 | 12 | 12 | 18 | 47 | 29 | 0.004 |
| **Norman** [208] | 1998 | 14 | 3 | 20.8 | 21.9 | 1.1 | NS |
| **Stammberger** [209] | 1998 | 40 | 3 | 44 | 46 | 2 | NS |
| **Oswald** [191] | 1998 | 9 | 3 to 6 | 46 | 50 | 4 | NS |
| **Gelb** [210] | 1999 | 6 | 27 | 35 | 59 | 24 | Unknown |
| **O'Brien** [211] | 1999 | 41 | 3 to 6 | 33 | 40 | 7 | 0.07 |
| **Geddes** [212] | 2000 | 24 | 12 | 36 | 45 | 9 | 0.11 |
| **Homan** [185] | 2001 | 36 | 6 | 38.7 | 43.1 | 4.4 | 0.0046 |
| **Bloch** [213] | 2002 | 115 | 3 | 40 | 43 | 3 | <0.01 |
| **Goldstein** [214] | 2003 | 28 | 12 | 35 | 37 | 2 | NS |
| **Ciccone** [215] | 2003 | 250 | 6 | 34 | 39 | 5 | <0.001 |
| **Tutic** [216] | 2004 | 21 | 6 | 37 | 40 | 3 | NS |
| **Meyers** [198] | 2004 | 20 | 6 | 16 | 27 | 11 | Unknown |
| **Hardoff** [217] | 2005 | 35 | 12 | 44.2 | 52.7 | 8.5 | NS |
| **Mineo** [218] | 2006 | 30 | 12 | 50.1 | 59.3 | 9.2 | <0.01 |
| **Weder** [219] | 2009 | 250 | 6 | 39.4 | 44.9 | 5.5 | NS |
| **Cremona** [180] | 2011 | 14 | Unknown | 27 | 37 | 10 | 0.08 |
| **Layton** [220] | 2015 | 10 | 7 | 31 | 33 | 2 | 0.29 |
| **Ginsburg** [221] | 2015 | 91 | 12 | 28.6 | 33.8 | 5.2 | <0.001 |
| **Clarenbach** [222] | 2015 | 14 | 3 | 35 | 40 | 5 | 0.061 |
| **Sievi** [223] | 2016 | 12 | 3 | 34 | 37.7 | 3.7 | Unknown |
| **Caviezel** [224] | 2018 | 30 | 3 | 31.3 | 26.7 | -4.6 | 0.686 |
| **Caviezel** [197] | 2018 | 33 | 3 | 15 | 24 | 9 | <0.001 |

*$DL_{CO}$ = Diffusing Capacity of the Lung for Carbon Monoxide, NS = not significant. Baseline and follow up $DI_{CO}$ is given in percentage of predicted. Due to variable reporting of confidence intervals (i.e. standard deviation, interquartile range, minimum-maximum) these values are not reported in this table.*

**Table S2** | $DL_{CO}$ before and after Endoscopic Lung Volume Reduction with Endobronchial Valves

| Study | Year | N (treated) | Interval (months) | Baseline $DL_{CO}$ (%pred) | Follow Up $DL_{CO}$ (%pred) | $\Delta DL_{CO}$ (absolute %) | P-value |
|---|---|---|---|---|---|---|---|
| **Toma** [160] | 2003 | 8 | 1 | 35.6 | 45.8 | 10.2 | 0.02 |
| **Snell** [188] | 2003 | 10 | 1 | 31 | 34.3 | 3.3 | 0.04 |
| **Yim** [225] | 2004 | 21 | 3 | 50.8 | 60.6 | 9.8 | 0.43 |
| **Hopkinson** [226] | 2005 | 19 | 1 | 35.9 | 40.9 | 5 | 0.02 |
| **Venuta** [189] | 2005 | 13 | 3 | 33 | 50 | 17 | 0.01 |
| **Wan** [227] | 2006 | 98 | 3 | 32.7 | 36.8 | 4.1 | 0.06 |
| **Chung** [228] | 2010 | 7 | 3 | 38 | 38 | 0 | 0.34 |
| **Kotecha** [229] | 2011 | 16 | 1 | 34.7 | 39.5 | 4.8 | 0.02 |
| **Hillerdal** [186] | 2014 | 15 | 6 | 28 | 38 | 10 | Unknown |
| **Klooster** [32] | 2015 | 22 | 6 | 40.9 | 44.2 | 3.3 | 0.021 |
| **Park** [230] | 2015 | 43 | 6 | 31.6 | 34.3 | 2.7 | <0.05 |
| **Fiorelli** [231] | 2016 | 49 | 6 | 52 | 54.7 | 2.7 | 0.7 |
| **Fiorelli** [232] | 2017 | 33 | 3 | 58 | 59 | 1 | 0.91 |
| **Kemp** [34] | 2017 | 65 | 6 | 32.3 | 33.6 | 1.3 | 0.004 |
| **Criner** [33] | 2018 | 128 | 12 | 34.6 | 36.4 | 1.8 | 0.013 |

*$DL_{CO}$ = Diffusing Capacity of the Lung for Carbon Monoxide. Baseline and follow up $DI_{CO}$ is given in percentage of predicted. Due to variable reporting of confidence intervals (i.e. standard deviation, interquartile range, minimum-maximum) these values are not reported in this table.*

**Table S3** | $DL_{CO}$ before and after LVRS (in ml/min/mmHg)

| Study | Year | N (treated) | Interval (months) | Baseline $DL_{CO}$ (ml/min/mmHg) | Follow Up $DL_{CO}$ (ml/min/mmHg) | $\Delta DL_{CO}$ (absolute) | P-value |
|---|---|---|---|---|---|---|---|
| **Ferguson** [233] | 1998 | 18 | 3-6 | 10.59 | 10.19 | -0.40 | NS |
| **Albert** [181] | 1998 | 46 | 3 | 7.44 | 9.44 | 2 | <0.05 |
| **Fujimoto** [234] | 1999 | 12 | 6 | 11.2 | 14.5 | 3.3 | <0.05 |
| **Kuwahira** [235] | 2000 | 20 | 6 | 9.03 | 8.96 | -0.07 | NS |
| **Miller** [236] | 2005 | 54 | 6 | 7.58 | 8.69 | 1.11 | 0.144 |

*NS = Not significant*

**Table S4** | Variation in change in $DL_{CO}$ before and after Lung Volume Reduction Treatment

**4a. Absolute change in $DL_{CO}$ (%pred)**

| Study | Year | Treatment | n Treated) | $\Delta DL_{CO}$ (Abs. change in %pred) |
|---|---|---|---|---|
| **Oswald** [191] | 1998 | LVRS | 9 | 4 (-9 to +34) |
| **Gelb** [207] | 1999 | LVRS | 6 | 23 (-6.0 to +29) |
| **Wan** [227] | 2006 | BLVR | 98 | 17.2±52 |
| **Clarenbach** [222] | 2015 | LVRS | 14 | 5.0 [1.0 to 7.0] |
| **Kemp** [34] | 2017 | BLVR | 65 | 2.78±8.84 |
| **Criner** [184] | 2018 | BLVR | 128 | 1.8±8.44 |

**4b. Relative change in $DL_{CO}$ (%pred)**

| Study | Year | Treatment | n (Treated) | $\Delta DL_{CO}$ (%) |
|---|---|---|---|---|
| **Albert** [181] | 1998 | LVRS | 46 | 24±54 |
| **O'Brien** [211] | 1999 | LVRS | 41 | 8.5±45 |
| **Meyers** [198] | 2004 | LVRS | 20 | 70±82 |

**4c. Absolute change in $DL_{CO}$ (ml/min/mmHg)**

| Study | Year | Treatment | n (Treated) | $\Delta DL_{CO}$ (ml/min/mmHg) |
|---|---|---|---|---|
| **Homan** [185] | 2001 | LVRS | 36 | 0.96±1.831 |
| **Snell** [188] | 2003 | BLVR | 10 | 0.45 (-0.6 to 2.2) |

*Data represented as either mean±SD; median (min-max) or median [IQR]. LVRS=Lung Volume Reduction Surgery, BLVR=Bronchoscopic lung volume reduction.*

**Table S5** | p(A-a)$O_2$ gradient before and after Lung Volume Reduction Treatment

| Study | Year | Type LVR | N treat | Baseline p(A-a)$O_2$ gr (kPa) | Follow up p(A-a)$O_2$ gr (kPa) | Δ p(A-a)$O_2$ gr |
|---|---|---|---|---|---|---|
| **Snell** [188] | 2003 | BLVR | 10 | 3.2 | 3.2 | 0.0 |
| **Venuta** [189] | 2005 | BLVR | 13 | 2.5 | 3.3 | 0.8 |
| **Venuta** [237] | 2012 | BLVR | 40 | 3.4 | 3.4 | 0.0 |
| **Fiorelli** [231] | 2016 | BLVR | 49 | 4.2 | 3.3 | -0.9 |
| **Fiorelli** [232] | 2017 | BLVR | 33 | 3.9 | 4.1 | 0.2 |
| **Cooper** [29] | 1995 | LVRS | 20 | 4.8 | 4.2 | -0.6 |
| **Cooper** [28] | 1996 | LVRS | 150 | 4.7 | 4.2 | -0.5 |
| **Sciurba** [187] | 1996 | LVRS | 20 | 4.2 | 4.5 | 0.3 |
| **Roue** [238] | 1996 | LVRS | 13 | 5.3 | 5.0 | -0.3 |
| **Ferguson** [233] | 1998 | LVRS | 18 | 6.7 | 7.1 | 0.4 |
| **Date** [239] | 1998 | LVRS | 39 | 3.4 | 3.1 | -0.3 |
| **Cassina** [240] | 1998 | LVRS | 30 | 5.0 | 4.4 | -0.6 |
| **Albert** [181] | 1998 | LVRS | 46 | 4.0 | 4.1 | 0.1 |
| **Gelb** [207] | 1998 | LVRS | 12 | 3.9 | 3.6 | -0.3 |
| **Norman** [208] | 1998 | LVRS | 14 | 4.8 | 3.7 | -1.1 |
| **Stammberger** [209] | 1998 | LVRS | 40 | 4.1 | 3.9 | -0.2 |
| **Oswald** [191] | 1998 | LVRS | 9 | 3.2 | 3.4 | 0.2 |
| **Shade** [241] | 1999 | LVRS | 33 | 3.6 | 3.2 | -0.4 |
| **Fujimoto** [234] | 1999 | LVRS | 12 | 4.2 | 3.6 | -0.6 |
| **Leyenson** [242] | 2000 | LVRS | 42 | 3.0 | 4.6 | 1.6 |
| **Malthaner** [243] | 2000 | LVRS | 24 | 3.9 | 4.7 | 0.8 |
| **Geddes** [212] | 2000 | LVRS | 24 | 3.9 | 2.8 | -1.1 |
| **Pompeo** [244] | 2000 | LVRS | 30 | 4.1 | 3.8 | -0.3 |
| **Kuwahira** [235] | 2000 | LVRS | 20 | 4.1 | 3.8 | -0.3 |
| **Cassart** [245] | 2001 | LVRS | 11 | 5.0 | 4.4 | -0.6 |
| **Bloch** [213] | 2002 | LVRS | 115 | 5.0 | 4.9 | -0.1 |
| **Ciccone** [215] | 2003 | LVRS | 250 | 4.5 | 3.9 | -0.6 |
| **Takayama** [246] | 2003 | LVRS | 23 | 3.8 | 3.2 | -0.6 |
| **Tutic** [216] | 2004 | LVRS | 21 | 5.8 | 4.9 | -0.9 |
| **Meyers** [198] | 2004 | LVRS | 20 | 4.8 | 4.7 | -0.1 |
| **Hillerdal** [186] | 2005 | LVRS | 53 | 4.5 | 4.5 | 0 |

**Table S5** | *Continued*

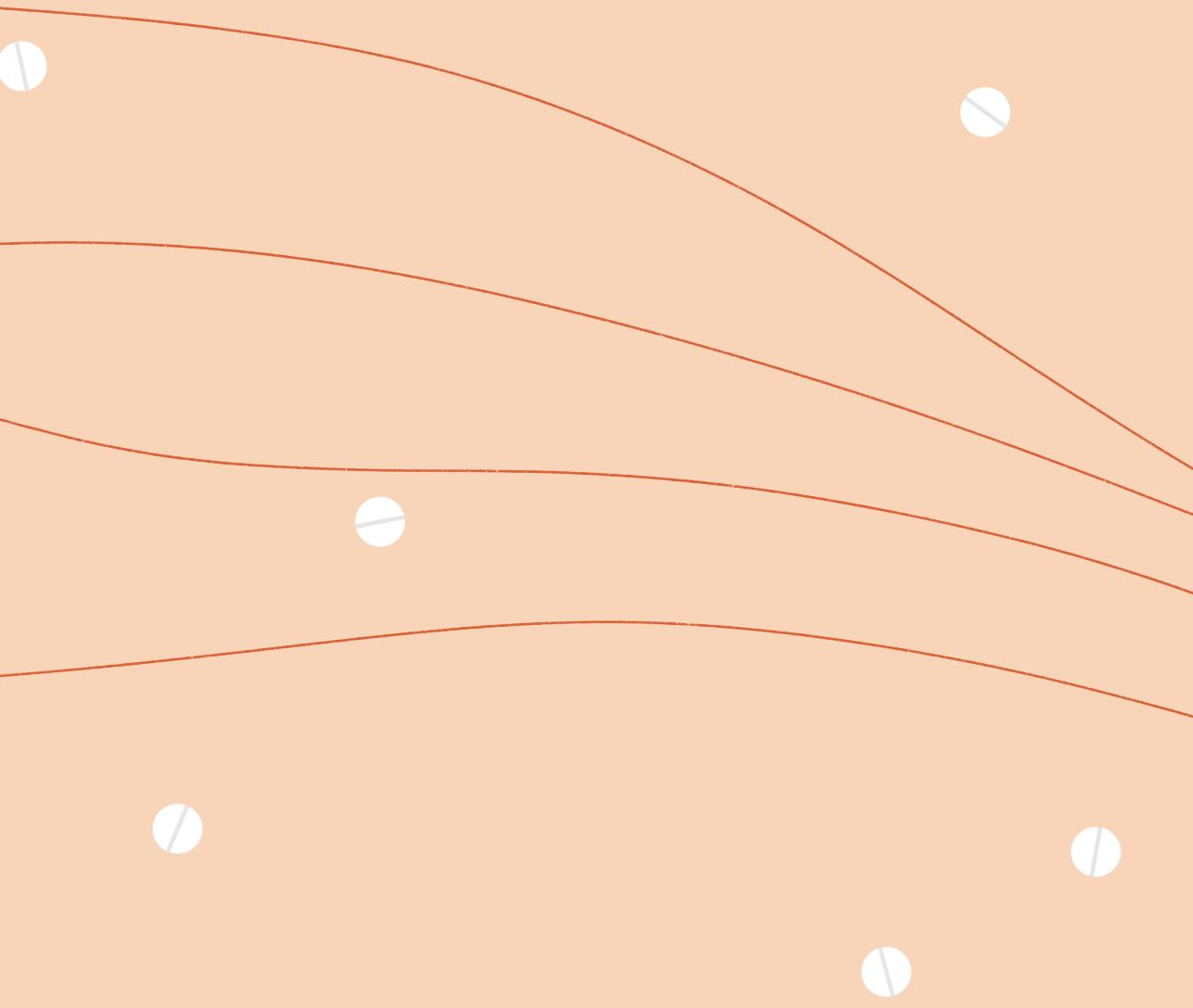
| Study | Year | Type LVR | N treat | Baseline p(A-a)$O_2$ gr (kPa) | Follow up p(A-a)$O_2$ gr (kPa) | Δ p(A-a)$O_2$ gr |
|---|---|---|---|---|---|---|
| **Cremona** [180] | 2011 | LVRS | 14 | 4.3 | 4.2 | -0.1 |
| **Pompeo** [247] | 2012 | LVRS | 63 | 4.1 | 4.0 | -0.1 |
| **Dauriat** [248] | 2016 | LVRS | 52 | 4.4 | 4.0 | -0.4 |
| **Caviezel** [197] | 2018 | LVRS | 30 | 5.2 | 4.7 | -0.5 |
| **You** [249] | 2018 | LVRS | 15 | 0.3 | 0.6 | 0.3 |

*LVRS=Lung Volume Reduction Surgery. BLVR = Bronchoscopic Lung Volume Reduction.*

**Table S6** | Change in $DL_{CO}$, $PaO_2$ and p(A-a)$O_2$ gradient before and after LVRT

| Study | Year | Type LVR | N Treat | Δ$DL_{CO}$ (%pred) | Δ $PaO_2$ (kPa) | BaselinE p(A-a)$O_2$ grad (kPa) | Follow uP p(A-a)$O_2$ grad (kPa) | Δp(A-a)$O_2$ gradient |
|---|---|---|---|---|---|---|---|---|
| **Snell** [188] | 2003 | BLVR | 10 | 3.3 | 0.15 | 3.2 | 3.2 | 0 |
| **Venuta** [189] | 2005 | BLVR | 13 | 17 | -0.4 | 2.5 | 3.3 | 0.8 |
| **Fiorelli** [231] | 2016 | BLVR | 49 | 2.7 | 1 | 4.2 | 3.3 | -0.9 |
| **Fiorelli** [232] | 2017 | BLVR | 33 | 1 | 0 | 3.9 | 4.1 | 0.2 |
| **Sciurba** [187] | 1996 | LVRS | 20 | 3 | 0.3 | 4.2 | 4.5 | 0.3 |
| **Gelb** [207] | 1998 | LVRS | 12 | 29 | 1.3 | 3.9 | 3.6 | -0.3 |
| **Norman** [208] | 1998 | LVRS | 14 | 1.1 | 1.1 | 4.8 | 3.7 | -1.1 |
| **Stammberger** [209] | 1998 | LVRS | 40 | 2.0 | 0.8 | 4.1 | 3.9 | -0.2 |
| **Oswald** [191] | 1998 | LVRS | 9 | 4.0 | 0 | 3.2 | 3.4 | 0.2 |
| **Geddes** [212] | 2000 | LVRS | 24 | 9 | 0.4 | 3.9 | 2.8 | -1.1 |
| **Bloch** [213] | 2002 | LVRS | 115 | 3 | 0.3 | 5 | 4.9 | -0.1 |
| **Ciccone** [215] | 2003 | LVRS | 250 | 5 | 1.1 | 4.5 | 3.9 | -0.6 |
| **Tutic** [216] | 2004 | LVRS | 21 | 3 | 0.5 | 5.8 | 4.9 | -0.9 |
| **Meyers** [198] | 2004 | LVRS | 20 | 11 | 1.2 | 4.8 | 4.7 | -0.1 |
| **Cremona** [180] | 2011 | LVRS | 14 | 10 | 0.7 | 4.3 | 4.2 | -0.1 |
| **Caviezel** [197] | 2018 | LVRS | 30 | -4.6 | 0.4 | 5.2 | 4.7 | -0.5 |

*LVRS=Lung Volume Reduction Surgery. BLVR = Bronchoscopic Lung Volume Reduction.*



CHAPTER

4

# Endobronchial valve treatment in emphysema patients with a very low diffusing capacity

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## Abstract

**Background:** For selected patients with severe emphysema, bronchoscopic lung volume reduction with endobronchial valves (EBV) is recognized as an additional treatment option. In most trials investigating EBV treatment, patients with a very low diffusing capacity ($DL_{CO}$) were excluded from participation.

**Objectives:** Our goal was to investigate whether EBV treatment in patients with emphysema with a very low $DL_{CO}$ is safe and effective.

**Methods:** This was a single-center retrospective analysis including patients with emphysema and a $DL_{CO}$ ≤20%pred who underwent EBV treatment. Follow-up was performed 6 months post-treatment. Outcome parameters were compared to a historical matched control group ($DL_{CO}$>20%pred, matched for sex, age, forced expiratory volume in 1s [$FEV_1$], and residual volume [RV]).

**Results:** Twenty patients (80% female, 64±6 years, $FEV_1$ 26±6%pred, RV 233±45%pred, $DL_{CO}$ 18±1.6%pred) underwent EBV treatment. At 6 months follow-up, we found a statistically significant improvement in $FEV_1$ (0.08 ± 0.12 L), RV (–0.45 ± 0.95 L), 6 min walk distance (38±65 m), and St. George's Respiratory Questionnaire (–12±13 points). With the exception of $FEV_1$, all exceeded the minimal clinically important difference. The most common serious adverse event was a pneumothorax requiring intervention (15%). There were no significant differences in outcome compared to the $DLC_O$>20%pred control group.

**Conclusions:** In this single-center retrospective analysis, we showed statistically significant and clinically relevant improvements in lung function, exercise capacity, and quality of life up to 6 months after EBV treatment in emphysema patients with a $DL_{CO}$ ≤20% (14– 20%) of predicted with no increased risk of serious adverse events.


## Introduction

In advanced chronic obstructive pulmonary disease (COPD), breathlessness, impaired exercise capacity, and poor quality of life are common despite optimal standard therapy [12].For selected patients with advanced COPD, bronchoscopic lung volume reduction with endobronchial valves (EBV) is recognized as an additional treatment option [1]. Prerequisites for this treatment are the presence of emphysema, severe hyperinflation, and absence of collateral ventilation between the target lobe and ipsilateral lobe(s) [36]. EBV treatment has emerged in recent years as a less invasive alternative for lung volume reduction surgery and has been shown to improve lung function, exercise capacity, and quality of life [32-35, 65].

In most research investigating EBV treatment, patients with a very low diffusing capacity of the lungs for carbon monoxide ($DL_{CO}$) were excluded from participating. This is mostly due to the results of the National Emphysema Treatment Trial (NETT), a large international multicenter trial comparing lung volume reduction to standard of care, where a subgroup

of high-risk patients was identified with an increased postoperative mortality rate [30, 250]. These high-risk patients were defined by having a forced expiratory volume in 1 s ($FEV_1$) of 20% or less of the predicted value combined with either a homogeneous distribution of emphysema or a $DL_{CO}$ of ≤20% of predicted (%pred). However, a recent retrospective trial investigating lung volume reduction surgery in patients with a $DL_{CO}$ of <20%pred showed positive effects of treatment with no increased mortality rate (90-day mortality 0%) [197].

To our knowledge, no study evaluating outcomes in patients with a very low $DL_{CO}$ undergoing EBV-treatment has been published so far. Our goal was to investigate whether patients with COPD and a very low $DL_{CO}$ have the same clinical benefits as patients with a $DL_{CO}$ above 20%pred and whether these patients are at increased risk of serious adverse events (SAEs). Furthermore, in the group of patients with a very low $DL_{CO}$, we performed subanalyses for multiple patient characteristics relating to reduced oxygen uptake and emphysema distribution to assess whether these were associated with differences in outcome of EBV treatment.



## Material and Methods

### *Study Design and Population*

This was a single-center retrospective analysis including patients with COPD and a $DL_{CO}$ ≤20%pred who underwent bronchoscopic lung volume reduction with EBV at our hospital between April 2016 and October 2018. All patients with a $DL_{CO}$ ≤20%pred who were treated in our hospital and registered in the BREATH-NL Registry (NCT02815683) or participated in a clinical trial (NCT02022683) were included. A historical control group of patients treated in our hospital with a $DL_{CO}$ ≥20%pred was selected from the BREATH-NL Registry. These control patients were matched for sex, age, $FEV_1$, and residual volume (RV). During the selection process, all outcome parameters were blinded. All subjects signed informed consent.

### *Measurements*

Post-bronchodilator spirometry, body plethysmography, and diffusion capacity were measured using the Jaeger MasterScreen™ (CareFusion, Germany) and were performed according to the ATS/ERS guidelines using the reference values from the European Community for Coal and Steel [251-253]. Spirometry and body plethysmography were performed at baseline and 6 months after treatment. The 6-min walk test was performed at baseline and 6 months and done in accordance with ATS recommendations [254]. The St. George's Respiratory Questionnaire (SGRQ) was used to measure health-related quality of life [255] and was obtained at baseline and 6 months follow-up. Arterial blood gas analysis, high-resolution CT scan, quantitative CT analysis, and echocardiogram were performed at baseline.

*Treatment*

All bronchoscopic procedures were performed according to current best practice recommendations and all under general anesthesia [31]. A Chartis measurement (Chartis®, Pulmonx Corporation, Redwood City, CA, USA) was performed to assess collateral ventilation between the target lobe and ipsilateral lobe(s). In the absence of collateral ventilation, EBV (Zephyr® EBV, Pulmonx Corporation, Redwood City, CA, USA) were placed in all segments or subsegments of the target lobe.

*Responders*

A patient was considered a responder to treatment if the $FEV_1$, RV, 6 min walk distance (6MWD), or SGRQ improved more than the minimal clinically important difference (MCID) after treatment. The following MCIDs were used: relative change in $FEV_1$ ≥12%, a decrease in RV of ≥430 mL, an increase in 6MWD of ≥26 m, and a decrease of SGRQ total score of 4 or 7 points [256-260].

*Subanalyses*

Subanalyses were performed to assess whether there was a difference in outcome when patients (with a $DL_{CO}$ ≤20%pred) were divided into groups based on baseline partial pressure of oxygen in arterial blood on room air ($PaO_2$; ≥8.0 kPa [60 mm Hg] or <8.0 kPa), oxygen saturation ($StO_2$) post 6MWD (≥88 or <88%), distribution of emphysema (heterogeneous when difference between target and ipsilateral lobe voxels below –950 Hounsfield units on high-resolution CT scan ≥15 percentage point, otherwise homogeneous), or presence of pulmonary hypertension (right ventricular peak pressure <25 or ≥25 mm Hg on echocardiogram).

*Statistics*

A Wilcoxon signed ranks test was performed to evaluate the difference in lung function, exercise capacity, and quality of life between baseline and 6 months follow-up. A Mann-Whitney U test was performed for the comparison of outcome parameters between patients with a $DL_{CO}$ ≤20% vs. $DL_{CO}$ >20% and also for the subgroup analyses. When follow-up data ($FEV_1$, RV, 6MWD, or SGRQ) were missing, the patient was considered to be a non-responder. A *p* value of <0.05 was considered statistically significant. IBM SPSS Statistics version 23 (IBM, Armonk, NY, USA) was used for all analyses.

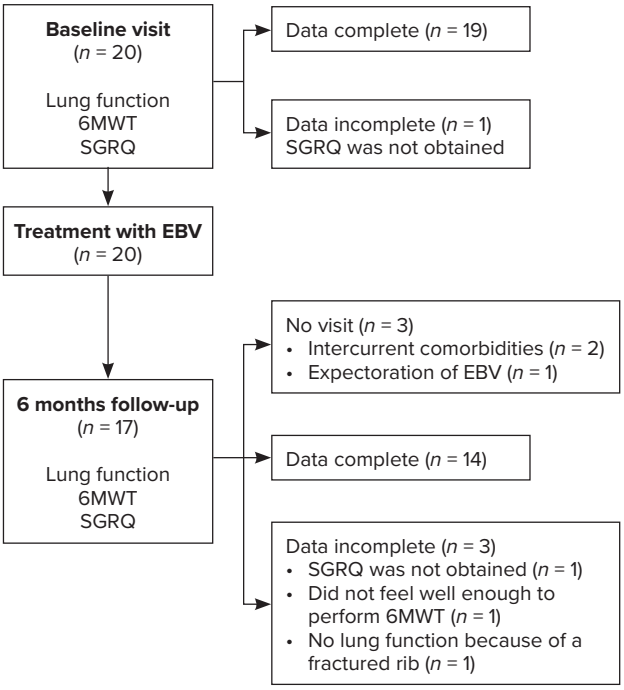


*Figure 1: Study flowchart for patients with a $DL_{CO}$ ≤20%pred. EBV: Endobronchial valve; SGRQ: St. George's Respiratory Questionnaire; 6MWT: 6-minute walk test.*

**Table 1** | Baseline characteristics

| Baseline characteristic | Patients with a $DL_{CO}$ ≤20%pred, (n=20) | Patients with a $DL_{CO}$ > 20%pred (historical matched control group, n=20) |
|---|---|---|
| Female – no. (%) | 16 (80%) | 16 (80%) |
| Age – yr | 64±6 | 62±7 |
| Body-mass index – kg/m² | 21±2.7 | 23±3.1 |
| Cigarette smoking – no. of pack years | 44±19 | 51±27 |
| $FEV_1$ | | |
| Liters | 0.58±0.14 | 0.61±0.13 |
| % of predicted | 23±4 | 24±4 |
| FVC | | |
| Liters | 2.15±0.74 | 2.30±0.48 |
| % of predicted | 70±17 | 76±15 |
| RV | | |
| Liters | 5.26±0.92 | 5.24±1.30 |
| % of predicted | 252±46 | 252±49 |
| TLC | | |
| Liters | 7.77±1.28 | 7.77±1.50 |
| % of predicted | 141±13 | 142±18 |

**Table 1** | *Continued*

| Baseline characteristic | Patients with a $DL_{CO}$ ≤20%pred, (n=20) | Patients with a $DL_{CO}$ > 20%pred (historical matched control group, n=20) |
|---|---|---|
| Ratio of RV to TLC - % | 68±7 | 67±5 |
| Carbon monoxide diffusing capacity | | |
| mmol/(min*kPa) | 1.49±0.27 | 2.31±0.65 |
| % of predicted value | 18±1.6 (range 14-20%) | 29±6 |
| Arterial blood gas – kPa | | |
| $PaO_2$ | 8.4±1.2 | 8.9±1.5 |
| $PaCO_2$ | 5.6±0.7 | 5.6±0.68 |
| $p(A\text{-}a)O_2$ gradient | 4.5±1.1 | 4.1±1.5 |
| 6-min walk test | | |
| Distance – meters | 287±91 | 320±82 |
| Pre-test oxygen saturation - % | 95±2 | 95±2 |
| Post-test oxygen saturation - % | 86±7 | 89±5 |
| Questionnaires | | |
| SGRQ – points | 58±14 | 57±13 |
| mMRC – points | | |
| 2 | 7 (35%) | 5 (25%) |
| 3 | 9 (45%) | 14 (70%) |
| 4 | 4 (20%) | 1 (5%) |
| HRCT findings | | |
| Target-lobe | | |
| RUL | 4 | 6 |
| RUL+RML | 0 | 0 |
| RML | 1 | 1 |
| RLL | 3 | 5 |
| LUL | 5 | 4 |
| LLL | 7 | 4 |
| Target-lobe volume – ml | 1698±439 | 1642±458 |
| Target-lobe voxels below -950 HU - % | 46±6 | 44±6 |
| Emphysema distribution – no. (%) | | |
| Homogeneous | 13 (65%) | 12 (60%) |
| Heterogeneous | 7 (35%) | 8 (40%) |

*Data represented as mean±SD unless otherwise specified. $FEV_1$ = forced expiratory volume in 1 second, FVC = forced vital capacity, RV = residual volume, TLC = total lung capacity, SGRQ = St George's Respiratory Questionnaire, mMRC = modified Medical Research Counsel, HRCT = high-resolution computed tomography, RUL = right upper lobe, RML = right middle lobe, RLL = right lower lobe, LUL = left upper lobe, LLL = left lower lobe. Heterogeneous emphysema was defined as a difference between the target lobe and ipsilateral lobe(s) ≥15% in voxels below -950 HU - % on HRCT. There were no statistically significant differences in baseline characteristics, with the exception of $DI_{CO}$ as per study design.*

## Results

Twenty patients with advanced COPD and a $DL_{CO}$≤20%pred underwent EBV treatment at our hospital (80% female, 58 ± 8 years, $FEV_1$ 26 ± 6%pred, RV 233 ± 45%pred). See study flowchart in Figure 1, and baseline characteristics in Table 1. Except for $DL_{CO}$ ($p$<0.001), there were no significant differences between baseline characteristics for the patient group with a $DL_{CO}$≤20%pred and the control group with a $DL_{CO}$ >20%pred (Table 1). At 6 months follow-up, there was a statistically significant improvement in all lung function parameters, 6MWD, and the SGRQ total score compared to baseline measurements (Table 2). RV (–0.45 ± 0.95 L), 6MWD (38± 65 m), and SGRQ score (–12 ± 13 points) improved more than the MCID. This was not the case for $FEV_1$ (0.08± 0.12 L). Responder rates at 6 months for the patient group with a $DL_{CO}$ ≤20%pred for $FEV_1$, RV, SGRQ (–4 points), SGRQ (–7 points), and 6MWD were 45, 40, 65, 50, and 45%, respectively (Figure 2). There were no statistically significant differences in lung function parameters, 6MWD, SGRQ total score, and responder rate between the patient group with a $DL_{CO}$ ≤20%pred and the control group with a $DL_{CO}$ >20%pred (Table 2). No patients died in both the group of patients with a $DL_{CO}$ ≤20%pred and the control group during 6 month follow-up. In the group of patients with a $DL_{CO}$ ≤20%pred, a pneumothorax, for which a chest tube insertion was needed, did occur in 3 cases (15%), all within 4 days after the procedure.



**Table 2** | Change in lung function, 6MWD and SGRQ total score after EBV-treatment for patients with a $DL_{CO}$≤20% of predicted and patients with a $DL_{CO}$>20% of predicted.

| Variable | Patients with $DL_{CO}$≤20% 6 months FU n=17 | Patients with $DL_{CO}$>20% 6 months FU n=19 | $DL_{CO}$ ≤20% vs >20% P value |
|---|---|---|---|
| Δ $FEV_1$ - Liters (relative change % ) | +0.08±0.12 (14±23)* | +0.18±0.16 (28±20) | 0.09 |
| Δ FVC - Liters (relative change %) | +0.28±0.41 (15±22)* | +0.48±0.60 (22±25) | 0.40 |
| Δ RV - Liters (relative change % ) | -0.45±0.95 (-9±18)* | -0.74±0.78 (-13±14) | 0.50 |
| Δ TLC - Liters (relative change % ) | -0.25±0.69 (-3±9)* | -0.38±0.52 (-5±6) | 0.82 |
| Δ RV/TLC - % | -5±7* | -6±7 | 0.53 |
| Δ6MWD - meters | +37±67* | +40±83 | 0.93 |
| ΔSGRQ - points | -12±14* | -10±16 | 0.71 |

*Data represented as mean±SD. FU = follow up, MCID= minimal clinically important difference, $FEV_1$ = forced expiratory volume in 1 second, FVC = forced vital capacity, RV = residual volume, TLC = total lung capacity, SGRQ = St George's Respiratory Questionnaire. * signifies significant improvement within the $DL_{co}$ < 20% group over 6 months p<0.05. There were no significant differences between change in outcomes 6 months after treatments between patients with a $DL_{CO}$≤20% and the control group ($DL_{CO}$>20%).*

In one of these cases, temporary removal of EBV and video-assisted thoracic surgery was additionally performed to resolve the pneumothorax. Three other patients had a small

pneumothorax not requiring intervention. Three patients developed a COPD exacerbation requiring hospital admission (15%). Three patients (15%) required additional bronchoscopies for valve replacement. One patient (5%) required removal of all valves because of valve migration and consequently loss of atelectasis due to extensive granulation tissue. No pneumonias were reported. No statistically significant differences were found for SAEs between the patients with a $DL_{CO}$≤20%pred and the control group (Table 3). Subgroup analyses for patients with a $DL_{CO}$≤20%pred divided into groups based on emphysema distribution (homogeneous n=11; heterogeneous n=5), baseline $PaO_2$ (≥8.0 kPa n=11; <8.0 kPa n=5), baseline $StO_2$ after 6-min walk test (≥88% n=9; <88% n=7) and presence of pulmonary hypertension on baseline echocardiography (RV peak pressure <25 mm Hg n=6; RV peak pressure ≥25 mm Hg n=10) revealed no statistically significant differences for change in lung function parameters, SGRQ scores, and 6MWD at 6 months follow-up, with the exception of improvement of forced vital capacity (FVC) in participants without pulmonary hypertension versus participants with pulmonary hypertension (ΔFVC +0.53 ± 0.29 L vs. +0.14 ± 0.42 L, *p*=0.045).



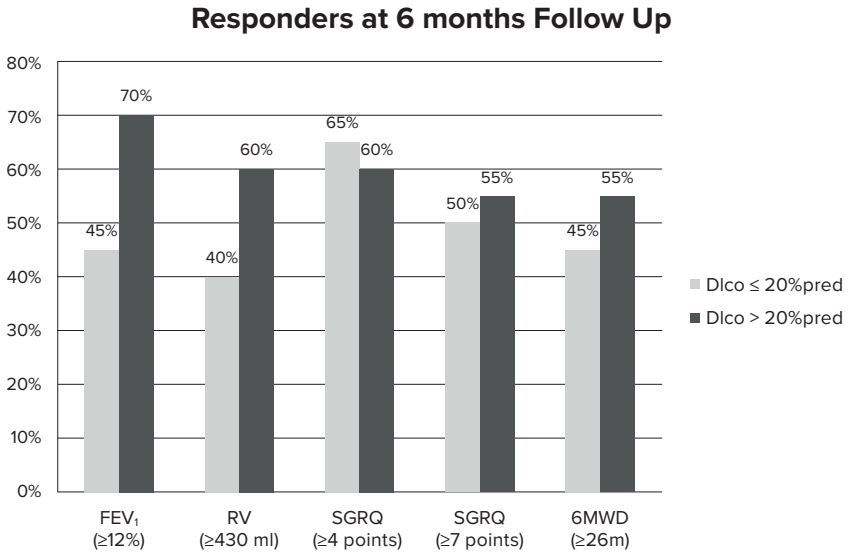


*Figure 2: Responder rates at 6 months follow-up for patients with a $DL_{CO}$≤20%pred (n=20) and $DL_{CO}$>20%pred (n=20). Responders were defined as having an improvement equal to or greater than the minimal clinically important difference for $FEV_1$ (≥12%) [256], RV (≥430 ml) [257], SGRQ (≥4 points) [258], SGRQ (≥7 points) [260], or 6MWD (≥26 m) [259]. There were no significant differences in responder rates for patients with a $DL_{CO}$ ≤20%pred and $DL_{CO}$ > 20%pred. $FEV_1$, forced expiratory volume in 1 s; RV, residual volume; 6MWD, 6 min walk distance; SGRQ, St. George's Respiratory Questionnaire.*

**Table 3** | Serious adverse events (SAE's) during six months follow up for patients with a $DL_{CO}$≤20% (n=20) and patients with a $DL_{CO}$>20%pred (n=20) and reported SAE's in RCT's investigating bronchoscopic lung volume reduction with endobronchial valves with a 3 to 12 month follow up.

| Serious Adverse Event | SAE's in patients with a $DL_{CO}$≤20% (n=20) n (%) | SAE's in patients with a $DL_{CO}$>20%pred (n=20) n (%) | Reported SAE's in the literature* min - max % |
|---|---|---|---|
| Pneumothorax | | | |
| Requiring chest tube drainage | 3 (15) | 2 (10) | 14.7 - 29.6 |
| Hospital admission for COPD exacerbation | 3 (15) | 1 (5) | 9.8 - 34.9 |
| Revision bronchoscopy | | | |
| For replacement or temporal removal of valve(s) | 3 (15) | 5 (25) | 6 - 20 |
| For permanent removal of valves | 1 (5) | 1 (5) | 1.5 - 20.5 |
| Pneumonia | 0 (0) | 2 (10) | 0 - 10 |
| Death | 0 (0) | 0 (0) | 1.5 - 10 |

*There were no statistically significant differences between SAE's for patients with a $DL_{CO}$≤20% and patients with a $DL_{CO}$>20%pred. * [32-35, 65]*



## Discussion/Conclusion

To our knowledge, this is the first study investigating EBV treatment in COPD patients with a very low $DL_{CO}$, that is, 20%pred or lower. We found a statistically significant improvement of lung function, 6MWD, and quality of life 6 months after EBV treatment. Improvement of RV, 6MWD, and SGRQ score were greater than the established MCID. Furthermore, there were no statistically significant differences in change in lung function, 6MWD, SGRQ, and responder rates and SAEs between the low $DL_{CO}$ group and the matched control group with a $DL_{CO}$>20%pred. The most common SAE was a pneumothorax requiring chest drainage (15%). Subanalyses of patients with a $DL_{CO}$≤20%pred divided into groups based on baseline characteristics that associate with reduced oxygen uptake and emphysema distribution showed no relevant differences on these outcomes. There was a trend towards a larger increase in $FEV_1$ in patients with a $DL_{CO}$ >20 vs. ≤20%pred (+0.18 ± 0.16 vs. +0.08 ± 0.12, $p$=0.08) and a higher responder rate for $FEV_1$ in the $DL_{CO}$ >20%pred group ($FEV_1$ 70 vs. 45%, $p$=0.11), but notably this was not reflected in a greater improvement in exercise capacity (6MWD) or quality of life (SGRQ). A recently published pooled analysis of 6 randomized controlled trials investigating EBV treatment (in patients with a $DL_{CO}$≥20%pred) showed an improvement in $FEV_1$ (+21.8% relative increase), RV (–0.58 L), 6MWD (+49 m), and SGRQ score (–9.1 points) 3–12 months after EBV treatment [26]. These results are somewhat better than our 6-month follow-up results for patients with a $DL_{CO}$ ≤20%pred ($FEV_1$ +16% relative increase, RV–0.45 L, 6MWD +38 m, SGRQ –12 points). This may be explained by the fact that

only patients with heterogeneous emphysema were included in 4 of the 6 trials, whereas in our study, 65% of patients with a $DL_{CO}$≤20%pred had a homogeneous distribution of emphysema. The responder rates for $FEV_1$, RV, SGRQ (–4 points), and 6MWD for patients with a $DL_{CO}$ ≤20%pred at 6 months follow-up were 45, 40, 65, and 45%, respectively. The responder rates are within the range of responder rates published in recent RCTs ($FEV_1$ 37–72%, SGRQ 56–79%, and 6MWD 42–87%) [32-35], with the exception of responder rate for RV, which is slightly lower (44–71%). It is important to note that our responder rates may be a conservative estimate, since all participants with missing data were considered to be non-responders. Furthermore, for patients with severe COPD, an MCID of 7 points on SGRQ total score has been shown to be more applicable to this patient group and treatment [260]. The incidence rate of SAEs in the patient group with a $DL_{CO}$ ≤20%pred was comparable to recent literature investigating EBV treatment (Table 3) [32-35, 65]. In studies investigating EBV treatment, patients with a very low $DL_{CO}$ were often excluded. This may not be surprising since $DL_{CO}$ has been associated with an increased likelihood of hypoxemia and is a known unfavorable prognostic factor in COPD [165, 166]. Furthermore, as mentioned in the introduction, the multicenter NETT trial investigating lung volume reduction surgery identified a group of high-risk patients with an $FEV_1$ <20%pred and either a homogeneous distributed emphysema or a $DL_{CO}$ ≤20% who had increased 30-day mortality rates (16%) [250]. However, patients fulfilling the NETT high risk criteria have more recently been demonstrated to be able to have good effects from lung volume reduction surgery with no increased mortality rate [197, 198]. Furthermore, EBV treatment in patients with a $FEV_1$ ≤20%pred has been shown to be safe and effective [261, 262], and our study shows good results for EBV treatment in patients with a $DL_{CO}$ ≤20%pred. The measurement of $DL_{CO}$ is used as an indication for functional gas exchange surface in the lung [263]. In emphysema, there is loss of gas exchange surface, and an inverse linear relation between $DL_{CO}$ and severity of emphysema on CT has been established [164]. However, in COPD, other factors such as ventilation/perfusion (V/Q) disturbances, inhomogeneous ventilation, and airway obstruction can influence the outcome of the $DL_{CO}$ measurement both negatively and positively [170, 171, 173]. The measured $DL_{CO}$ for a patient with COPD is therefore likely to be a balance of these factors. COPD is a heterogeneous disease, so while in one patient, the outcome of $DL_{CO}$ may be mainly due to loss of gas exchange surface, in the next patient, airway obstruction and V/Q disturbances may be the driving factors influencing $DL_{CO}$. We propose that the chance of successful EBV treatment in patients with a very low $DL_{CO}$ is related to the balance of factors causing the $DL_{CO}$ to be low. Factors we consider favorable in clinical practice are a high destruction level of the target lobe on chest CT and an $FEV_1$ larger than 20% of the predicted value. Factors we consider unfavorable are a homogeneous distribution of emphysema, significant target lobe perfusion, an important hypoxemia (*i.e.*, $PaO_2$<8.0 kPa or 60 mmHg), significant desaturation during exercise, and pulmonary hypertension. We take every factor into account, and no single factor is an absolute contraindication. It is important to note that there is no scientific literature to support the use of these factors for clinical decision-

making. Our study did have some limitations. First of all, this is a retrospective analysis. However, we did include a well-matched control group with a significantly higher $DL_{CO}$ to compare outcome parameters to. Furthermore, to prevent selection bias as much as possible, all patients with a $DL_{CO}$ ≤20%pred who underwent EBV treatment in our hospital were included. Nevertheless, there were emphysema patients with a very low $DL_{CO}$, who were assessed but not accepted for EBV treatment. Another limitation is that our group of patients is relatively small. For the subgroup analyses that were performed, the number of patients was likely too small to exclude relevant statistically significant differences. Also, the factors for which subanalyses were performed are also factors we take into account in our clinical decision-making whether or not to treat an individual patient. However, since only a minority of patients with COPD who undergo EBV treatment have a $DL_{CO}$≤20%pred, it may be challenging to investigate a larger group of patients. Furthermore, there is a risk of bias because of missing data. Therefore, as mentioned above, with regard to responder rates, we considered participants to be non-responders if data was missing. Finally, since no measurement of $DL_{CO}$ or arterial blood gas analysis was performed during follow-up, no information is available on change in $DL_{CO}$ or gas exchange after EBV treatment. In conclusion, we found statistically significant and clinically relevant improvements in lung function, exercise capacity, and quality of life up to 6 months after EBV treatment in COPD patients with a $DL_{CO}$ ≤20%pred, with no increased risk of SAEs in this single-center retrospective analysis. No factors influencing the chance of a successful treatment could be identified in this group of participants. However, since the investigated subgroups were small, it is too soon to draw any definitive conclusions on the latter subject. It would be interesting to investigate whether long-term follow-up of EBV treatment is comparable for COPD patients with and without a very low $DL_{CO}$. Furthermore, future research investigating factors influencing the likeliness of successful EBV treatment in COPD patients with a very low $DL_{CO}$ could greatly help clinicians in deciding whether or not EBV treatment is suitable for their patient.



**Statement of ethics:** All patients signed informed consent and this study was approved by the Ethics Committee (NCT02815683 and NCT02022683).

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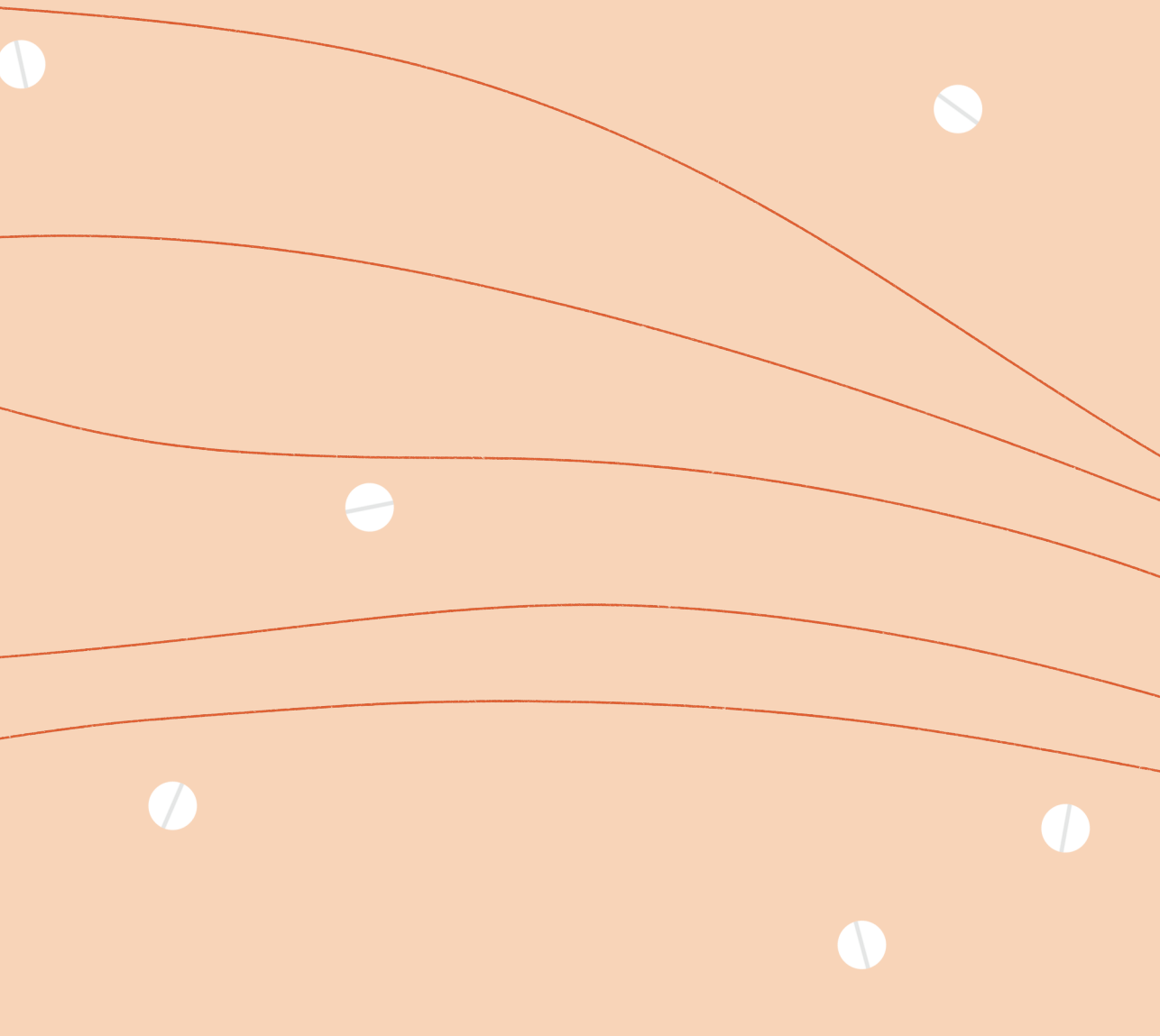
**Author Contributions:** M.v.D. contributed to the trial design, analysis of data, preparation of the “Results” section and tables, and the writing of the manuscript and is the guarantor of the manuscript. J.E.H. contributed to the analysis of the data and the discussion and revisions of the manuscript. K.K. contributed to the discussion and revisions of the manuscript. N.H.T.T.H. contributed to the discussion and revisions of the manuscript. H.A.M.K. contributed to the discussion and revisions of the manuscript. D.-J.S. contributed to the trial design and the discussion and revisions of the manuscript.



CHAPTER 5

# Change in dynamic hyperinflation after bronchoscopic lung volume reduction in patients with emphysema

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## Abstract

**Background and purpose:** In patients with severe emphysema, dynamic hyperinflation is superimposed on top of already existing static hyperinflation. Static hyperinflation reduces significantly after bronchoscopic lung volume reduction (BLVR). In this study, we investigated the effect of BLVR compared to standard of care (SoC) on dynamic hyperinflation.

**Methods:** Dynamic hyperinflation was induced by a manually paced tachypnea test (MPT) and was defined by change in inspiratory capacity (IC) measured before and after MPT. Static and dynamic hyperinflation measurements were performed both at baseline and 6 months after BLVR with endobronchial valves or coils (treatment group) or SoC (control group).

**Results:** Eighteen patients underwent BLVR (78% female, 57 (43–67) years, $FEV_1$ 25(18–37) %predicted, residual volume 231 (182–376) %predicted). Thirteen patients received SoC (100% female, 59 (44–74) years, $FEV_1$ 25 (19–37) %predicted, residual volume 225 (152–279) %predicted. The 6 months median change in dynamic hyperinflation in the treatment group was: + 225 ml (range − 113 to + 803) ($p$<0.01) vs 0 ml (− 1067 to + 500) in the control group ($p$=0.422) ); the difference between the groups was significant ($p$<0.01). An increase in dynamic hyperinflation was significantly associated with a decrease in residual volume ($r$ = − 0.439, $p$<0.01).

**Conclusion:** Bronchoscopic lung volume reduction increases the ability for dynamic hyperinflation in patients with severe emphysema. We propose this is a consequence of improved static hyperinflation.


5

## Introduction

In patients with severe emphysema chronic inflammation results in airway and lung parenchyma damage which is associated with reduced lung elastic recoil and increased airway resistance [8]. The combination of reduced elastic recoil and increased airway resistance can lead to a progressive increase of residual volume (RV) and end-expiratory lung volume (EELV), called static hyperinflation [8]. Increased hyperinflation can lead to dyspnea and consequently to reduced exercise capacity and poor quality of life [264]. Apart from static hyperinflation, exercise can lead to an additional increase in hyperinflation and a further decrease of the inspiratory capacity [8, 264]. This is called dynamic hyperinflation, which is superimposed on top of static hyperinflation. In patients with severe emphysema and severe static hyperinflation bronchoscopic lung volume reduction (BLVR) with endobronchial valves (EBV) or coils can lead to a statistically significant and clinically relevant reduction of static hyperinflation [26]. Furthermore, an improvement of dynamic hyperinflation has been demonstrated in a small group of patients after lung volume reduction surgery [52]. On the other hand, it could also be hypothesized that the improvement of static hyperinflation after bronchoscopic lung volume reduction leads to a

larger rest inspiratory capacity (IC), leaving more room for dynamic hyperinflation to occur. For this study our aim was to investigate if (and if so how) dynamic hyperinflation changed after bronchoscopic lung volume reduction compared to standard of care in patients with severe emphysema and severe static hyperinflation. Additionally, we aimed to investigate if there was an association between change in dynamic hyperinflation and change in parameters reflecting static hyperinflation and exercise tolerance.

## Methods

*Study design and population*

This was a single-center prospective cohort study in patients with severe emphysema who underwent a bronchoscopic lung volume reduction (BLVR) treatment with either endobronchial valves or coils or standard of care (SoC, no treatment) at the pulmonary department of the University Medical Center Groningen, the Netherlands. All subjects were clinically stable, on optimal medication and had stopped smoking at least 6 months before the study. All subjects participated in one of our bronchoscopic lung volume reduction trials (Clinical trial identifiers: NCT01421082; NCT01101958; NTR2876), which were approved by the local ethics committee. All subjects gave written informed consent. All subjects were included between June 2011 and July 2012. The baseline assessment measurements of this study population were part of an earlier publication [265]. From this baseline cohort patients were randomly invited for follow-up measurements for this study.



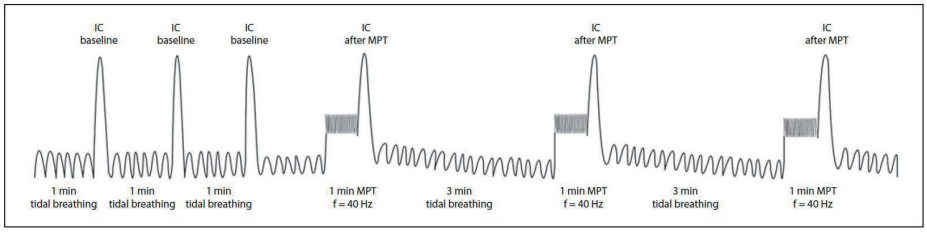



*Figure 1: Schematic overview of the dynamic hyperinflation measurement. IC: Inspiratory Capacity; MPT: Manually paced tachypnea; f: frequency (40 times/min).*

*Measurements*

All measurements were performed at baseline and 6 months after BLVR treatment or SoC. Subjects were instructed to use their regular inhalation medication. An additional 400 µg of salbutamol was administered 15 min 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 using the reference values from the European Community for Coal and Steel [251-253]. The 6-min walk test (6MWT) was performed according to ATS recommendations [254]. The St. George's Respiratory Questionnaire (SGRQ), and the modified Medical Research Council dyspnea scale (mMRC) were used to

measure quality of life and dyspnea severity, respectively [255, 266]. Dynamic hyperinflation was measured using a manually paced tachypnea (MPT) test using the breath-by-breath method (Oxycon Pro™, CareFusion, Germany) during a 15-min protocol (See Figure 1 for a schematic overview of the MPT procedure) [265]. During tidal breathing the subjects were asked to perform a minimum of 3 slow maximum inspirations (IC maneuver) with 1 min of normal tidal breathing between each maneuver. After this, the technician asked the subject to increase their breathing frequency (BF) to a rate of 40 times per min for 1 min. The technician used a visual real-time registration of the BF and provided the subject with vocal feedback of their BF. After 1 min of tachypnea, the subjects immediately performed an IC maneuver. The MPT procedure was repeated at least 3 times, with 3 min of normal tidal breathing between maneuvers. To establish the baseline IC ($IC_{baseline}$), we calculated the mean value of 3 reproducible IC's (within 150 ml). To establish the IC post tachypnea ($IC_{MPT}$) we calculated the mean value of the 2 highest and reproducible IC's (within 150 ml).

*Statistics*

Power was calculated based on mean change in IC of 0.5L (SD 0.4) [226]. With a power of 0.80 and alpha of 0.05 at least 12 patients per group needed to be included. Data was calculated as median (minimum–maximum) unless indicated otherwise. Dynamic hyperinflation was calculated by the absolute change in IC ($IC_{MPT}$ minus $IC_{baseline}$). A negative value of the absolute change in IC indicates a greater amount of dynamic hyperinflation. A Mann–Whitney U test was performed to compare baseline and follow-up lung function parameters, SGRQ and 6MWD. A Wilcoxon signed ranktest was used to compare baseline characteristics, change in lung function parameters, SGRQ and 6MWD between groups (BLVR vs. SoC). A Spearman correlation coefficient was calculated to assess the association between change in dynamic hyperinflation and change in static hyperinflation, airflow obstruction and 6 min walk distance. A $p$-value of $< 0.05$ was considered statistically significant. IBM SPSS Statistics version 23 (IBM, Armonk, NY, USA) was used for all analyses.

## Results

We studied 31 clinically stable patients with severe emphysema. Thirteen patients received SoC (100% female, 59 (44–74) years, $FEV_1$ 25 (19–37) %predicted, residual volume 225 (152–279) %predicted. Eighteen patients underwent BLVR (78% female, 57 (43–67) years, $FEV_1$ 25 (18–37) %predicted, residual volume 231 (182–376) %predicted. Of these, ten patients were treated with coils, eight patients received endobronchial valves. There were no statistically significant differences in baseline characteristics between the control and treatment group (Table 1). Dynamic hyperinflation changed significantly with – 225 ml (– 803 to + 113) ($p<0.01$) 6 months after BLVR. In the group of subjects receiving SoC, there was no significant change in dynamic hyperinflation (0 ml, range − 1067 to + 500). There was a significant difference in mean change of dynamic hyperinflation for the treatment group and control group ($p<0.01$). See Figure 2 for individual outcomes. There were no statistically significant differences in change in dynamic hyperinflation between subjects who were treated with

endobronchial valves [− 232 ml (− 803 to + 77)] and subjects who were treated with coils [− 170 ml (− 517 to + 113)]. In the treated subjects (n=18), there were statistically significant improvements in $FEV_1$, residual volume, and SGRQ total score compared to baseline (all $p<0.01$), which were not present in the SoC group. The between-group differences were all significantly different (Table 2). An increase in dynamic hyperinflation was significantly associated with a decrease in residual volume (rho=0.616, $p<0.001$), an increase in IC/TLC ratio (rho=− 0.418, $p<0.05$) and with an increase in 6MWD (rho=− 0.495, $p<0.01$) (see figure 3) for the treatment and control group combined.

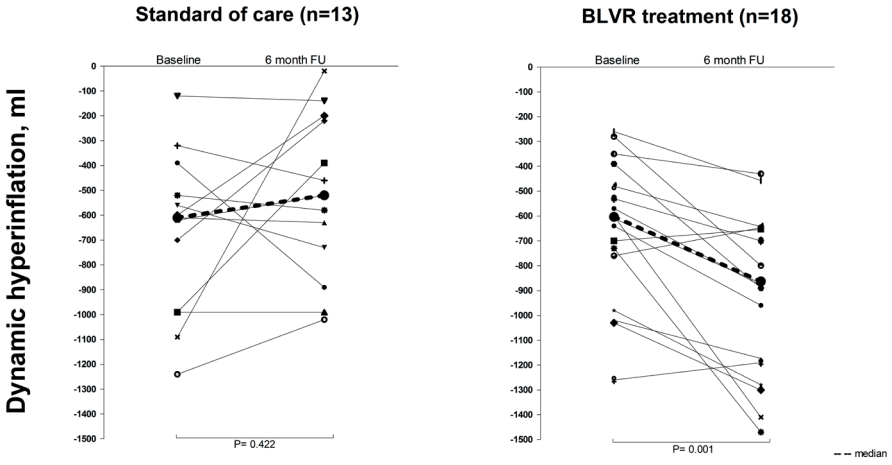



*Figure 2: Individual outcomes of dynamic hyperinflation at baseline and 6 months follow-up. BLVR: bronchoscopic lung volume reduction. De dotted line reflects the difference between the median dynamic hyperinflation at baseline and follow-up.*

**Table 1** | Baseline characteristics.

| Baseline characteristic | Treatment group n=18 | Control group n=13 | *p*-value |
|---|---|---|---|
| Female – no. (%) | 14 (78%) | 13 (100%) | 0.073 |
| Age – yr | 57 (43 to 67) | 59 (44 to 74) | 0.40 |
| Body-mass index – kg/m$^2$ | 23 (16 to 29) | 22 (18 to 26) | 0.32 |
| Cigarette smoking – no. Of pack years | 38 (5 to 80) | 40 (23 to 110) | 0.95 |
| $FEV_1$ | | | |
| Liters | 0.63 (0.45 to 1.01) | 0.69 (0.40 to 0.87) | 0.33 |
| % of predicted | 25(18 to 37) | 25 (19 to 37) | 0.56 |
| FVC | | | |
| Liters | 2.38 (1.28 to 3.71) | 2.01 (1.08 to 2.92) | 0.11 |
| % of predicted | 70 (44 to 101) | 63 (50 to 113) | 0.48 |
| RV | | | |
| Liters | 4.87 (2.93 to 7.71) | 4.10 (3.09 to 5.58) | 0.11 |
| % of predicted | 231 (182 to 376) | 225 (152 to 279) | 0.24 |
| TLC | | | |
| Liters | 7.48 (5.75 to 10.76) | 6.83 (5.27 to 7.92) | 0.08 |
| % of predicted | 134 (120 to 183) | 135 (114 to 150) | 0.56 |
| Ratio of RV to TLC - % | 65 (48 to 74) | 65 (52 to 75) | 0.97 |
| Ratio of IC to TLC - % | 20 (16 to 38) | 24 (16 to 37) | 0.38 |
| $R_{AW}$ | | | |
| kPa*S/L | 0.76 (0.33 to 1.21) | 0.67 (0.47 to 1.00) | 0.98 |
| % of predicted | 252 (109 to 404) | 225 (158 to 334) | 0.98 |
| Dynamic hyperinflation - ml | -610 (-1240 to -120) | -608 (-1260 to -260) | 0.90 |
| Carbon monoxide diffusing capacity | | | |
| mmol/(min*kPa) | 3.12 (1.93 to 5.52) | 2.76 (1.05 to 4.35) | 0.37 |
| % of predicted | 32 (24 to 69) | 35 (14 to 57) | 0.96 |
| Arterial blood gas (on room air) – kPa | | | |
| $PaO_2$ | 9.2 (7.1 to 11.9) | 8.5 (7.6 to 12.6) | 0.32 |
| $PaCO_2$ | 5.4 (4.4 to 6.9) | 5.2 (4.2 to 6.6) | 0.41 |
| 6-min walk test | | | |
| Distance – meters | 318 (160 to 485) | 400 (160 to 459) | 0.17 |
| Questionnaires | | | |
| SGRQ total score – points | 60 (25 to 79) | 59 (43 to 89) | 0.75 |
| mMRC – points | 3 (1-4) | 3 (2 to 4) | 0.83 |

*Data is represented as median (min to max) or number (%). $FEV_1$ = forced expiratory volume in 1 second, FVC = forced vital capacity, RV = residual volume, TLC = total lung capacity, $R_{aw}$ = airway resistance, SGRQ = St George's Respiratory Questionnaire, CCQ = Clinical COPD Questionnaire. There were no statistically significant differences between the treatment group and control group (Mann Whitney U test).*

**Table 2** | Median change in lung function, dynamic hyperinflation, 6MWD and SGRQ 6 months after BLVR treatment (n=18) or SoC (n=13).

| | **BLVR-treatment (n=18)** | **Standard of Care (n=13)** | **BLVR vs. SoC *p*-value** |
|---|---|---|---|
| ΔDH | | | |
| ml | -225 (-803 to +113)* | 0 (-500 to +1067) | 0.002 |
| relative change (%) | -33 (-186 to +15) | 0 (-128 to +988) | |
| $\Delta FEV_1$ | | | |
| ml | +110 (-130 to + 770)* | +20 (-10 to +13) | 0.034 |
| relative change (%) | +22 (-16 to +76) | +3 (-13 to 17) | |
| ΔIC (rest) | | | |
| ml | +200 (-350 to +1530)* | -33 (-430 to +270) | 0.010 |
| relative change (%) | +11 (-12 to +70) | -2 (-23 to +15) | |
| ΔRV | | | |
| ml | -765 (-3010 to +40) * | +40 (-140 to +280) | <0.001 |
| relative change (%) | -15 (-39 to +1) | +1 (-3 to 7) | |
| ΔTLC | | | |
| ml | -295 (-690+230) * | +40 (-290 to +260) | 0.002 |
| relative change (%) | -295 (-690 to +230) | +0.6 (-3.7 to +3.7) | |
| ΔRatio of RV to TLC - % | -8 (-25 to +1)* | +0 (-2 to +4) | <0.001 |
| ΔRatio of IC to TLC - % | +3 (-3 to +20) | -1 (-7 to +4) | 0.006 |
| Δ $R_{aw}$ (kPa*S/L) | -0.14 (-0.48 to +0.29)* | 0.01 (-0.15 to +0.29) | 0.06 |
| Δ6MWD | | | |
| meters | +55 (+8 to +233) * | -17 (-134 to +53) | <0.001 |
| ΔSGRQ | | | |
| Points | -11 (-53 to +6)* | -1 (-25 to +9) | 0.020 |

*BLVR = bronchoscopic lung volume reduction, DH = Dynamic hyperinflation, $FEV_1$= forced expiratory volume in 1 second, IC = Inspiratory capacity, RV = Residual volume, TLC = Total lung capacity, Raw = airway resistance, 6MWD = 6 min walk distance, SGRQ= St George's Respiratory Questionnaire. All changes between baseline and follow up were statistically significant for the treatment group, *p<0.05. There were no statistically significant changes between baseline and follow up for the SoC group measured by Mann Whitney U test.*

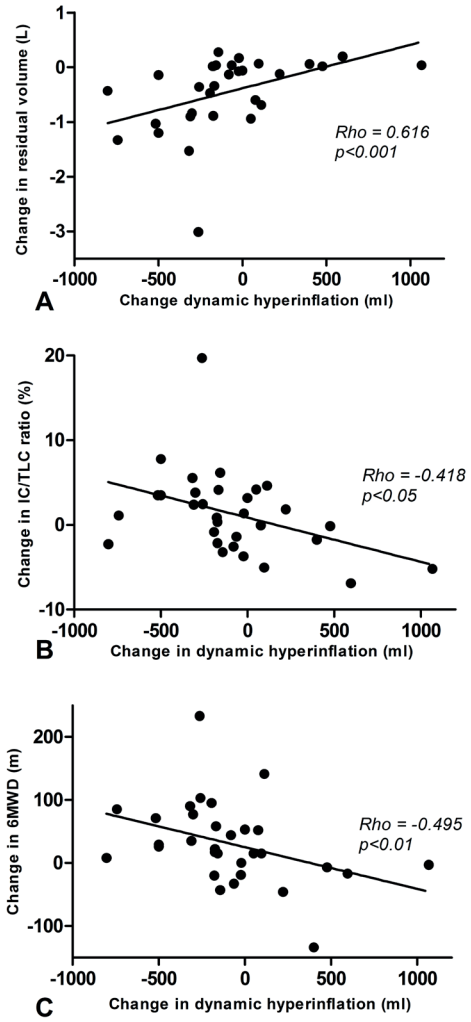
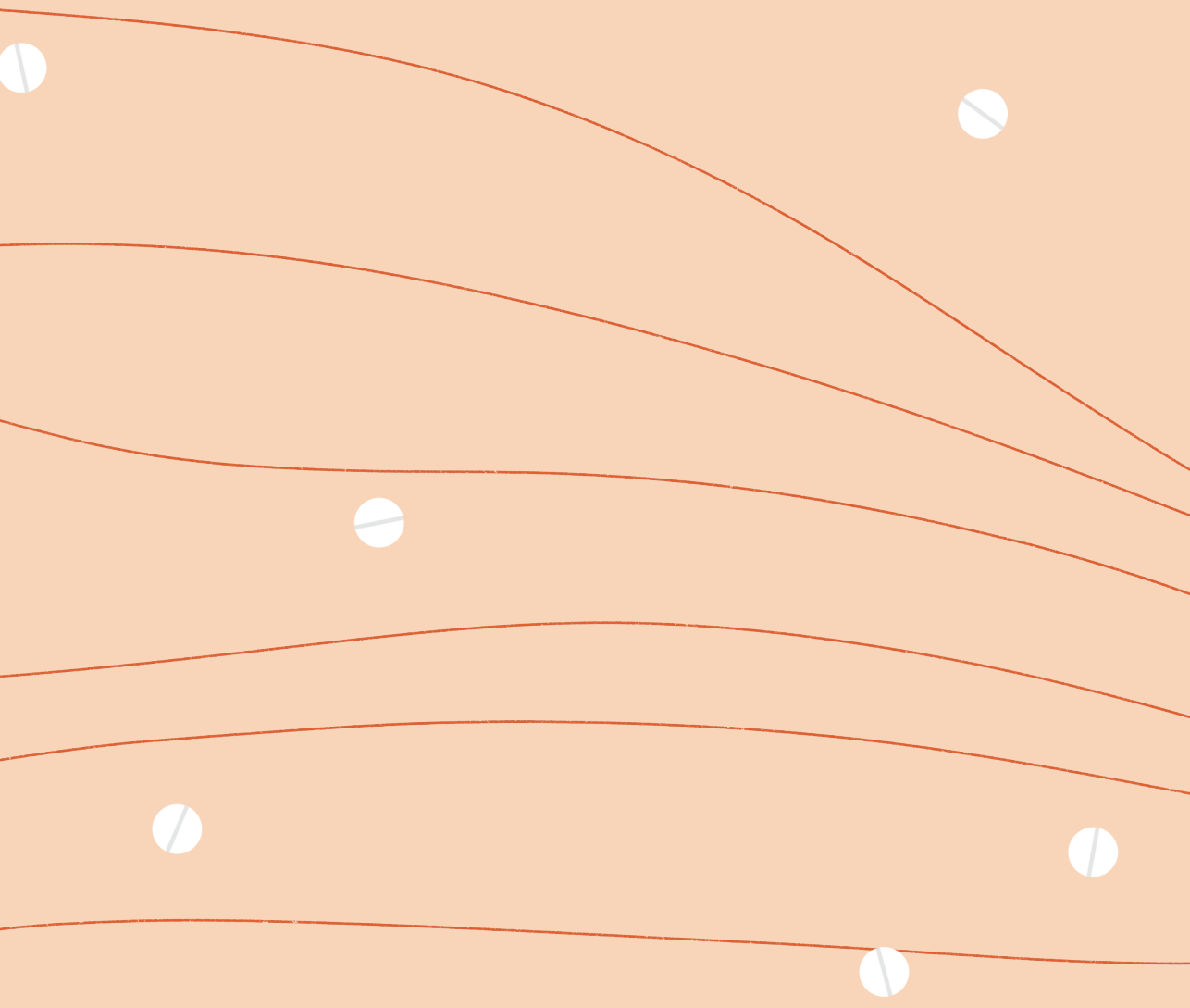



*Figure 3: A. Association between change in dynamic hyperinflation and change in residual volume. B. Association between change in dynamic hyperinflation and change in IC/TLC ratio. C. Association between change and 6MWD. RV residual volume; IC inspiratory capacity; TLC total lung capacity; 6MWD 6 min walk distance.*

## Discussion

In this single-center prospective cohort study, we investigated change in dynamic hyperinflation measured by a manually paced tachypnea test after lung volume reduction treatment with either endobronchial valves or coils compared to standard of care. We demonstrated a significant increase in dynamic hyperinflation after BLVR, which was not the case for standard of care. Change in dynamic hyperinflation showed a significant inverse association with change in residual volume and a significant association with change in IC/TLC ratio and change in 6 min walk distance. Our group has previously shown that performing a manually paced tachypnea test is feasible and safe in patients with severe COPD [265]. Interestingly, this previous study showed a negative association between dynamic hyperinflation and the 6MWD, *i.e.* more severe dynamic hyperinflation was associated with a better exercise tolerance. This is in line with the results of the current study where a larger increase of dynamic hyperinflation was associated with a larger increase in 6MWD. This may seem contrary to expectations, since dynamic hyperinflation is associated with a reduced exercise tolerance [267]. A possible explanation is that in this group of patients with severe static hyperinflation the inspiratory capacity is very low even in rest, and this leaves little space for dynamic hyperinflation to occur. When successful lung volume reduction treatment is performed and static hyperinflation decreases, the inspiratory capacity increases as does the ability to develop dynamic hyperinflation on tachypnea. Therefore, the increase in dynamic hyperinflation could even be seen as a positive marker of lung volume reduction treatment, since it indicates an improvement of the inspiratory capacity. Contrary to our results, several other studies have demonstrated a reduction of dynamic hyperinflation after lung volume reduction treatment [52, 220, 226, 268]. However, it is difficult to compare these studies to our own results because there are some important differences. First of all, different techniques were used, *i.e.* measurement of inspiratory capacity during rest and cardiopulmonary exercise testing (CPET) [52, 226, 268] and optoelectronic plethysmography [220]. Secondly, the breathing frequency was lower in the other studies compared to this study (25–28 times/min versus 40 times/min). And, perhaps most importantly, different definitions for dynamic hyperinflation were used. We defined dynamic hyperinflation as the change in inspiratory capacity after a period of tachypnea compared to resting breathing frequency. However, if end-expiratory lung volume at the end of the test is used to define dynamic hyperinflation, this may lead to a different outcome, because this value is also influenced by a change in static hyperinflation. Severity of airflow obstruction and static hyperinflation were comparable to our subjects in all studies. On a group level there was no change in dynamic hyperinflation in the control group after 6 months of standard of care. However, as shown in figure 2, on an individual level there were large variations in dynamic hyperinflation at baseline and follow-up. We propose that this is a reflection of real-life variability of dynamic hyperinflation in patients with COPD, most likely caused by changes in small airways disease such as mucous impaction and airway wall edema [267]. However, variability in the procedure can also play a role. Lahaije *et al*. found a repeatability coefficient of 8.5% for the MPT in patients with

moderate COPD [269]. If dynamic hyperinflation increases after bronchoscopic lung volume reduction, does this have therapeutic consequences? We believe the most important message is to reinforce adequate breathing techniques in our patients, focusing on slow, deep breaths during exercise. A meta-analysis showed that long-acting bronchodilators did have an effect on EELV during exercise, but this was a consequence of an improved IC in rest (*i.e.*, reduction in static hyperinflation) [270]. Interestingly, O'Donnel and colleagues demonstrated a protective effect of dynamic hyperinflation at lower exercise intensities by attenuation of the expiratory flow [271]. Our study does have some limitations. The group of subjects was relatively small. Especially since our results relating to dynamic hyperinflation are different from earlier studies, it would be interesting to investigate the change in dynamic hyperinflation by MPT in another, larger cohort of patients with COPD who undergo bronchoscopic lung volume reduction. Furthermore, the MPT test induces dynamic hyperinflation through tachypnea, but does not require exercise which is usually the trigger for DH to develop in patients with COPD. Excessive mechanical loading, ventilation of physiological dead space, arterial hypoxemia and early metabolic acidosis due to skeletal muscle deconditioning can lead to increased inspiratory neural drive to the respiratory muscles during exercise in COPD patients [272]. Furthermore, testing DH with CPET provides additional information on the influence of DH on exercise-induced dyspnea, cardiovascular function and muscle function [273]. A future study using both MPT and CPET to investigate change in dynamic hyperinflation would therefore be interesting.



CHAPTER 6

# Comparison of multiple diagnostic tests to measure dynamic hyperinflation in patients with severe emphysema treated with endobronchial coils

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## Abstract

**Purpose:** For this study, we aimed to compare dynamic hyperinflation measured by cardiopulmonary exercise testing (CPET), a 6-min walk test (6-MWT), and a manually paced tachypnea test (MPT) in patients with severe emphysema who were treated with endobronchial coils. Additionally, we investigated whether dynamic hyperinflation changed after treatment with endobronchial coils.

**Methods:** Dynamic hyperinflation was measured with CPET, 6-MWT, and an MPT in 29 patients before and after coil treatment.

**Results:** There was no significant change in dynamic hyperinflation after treatment with coils. Comparison of CPET and MPT showed a strong association (rho 0.660, $p<0.001$) and a moderate agreement (BA-plot, 202 ml difference in favor of MPT). There was only a moderate association of the 6-MWT with CPET (rho 0.361, $p$ 0.024).

**Conclusion:** MPT can be a suitable alternative to CPET to measure dynamic hyperinflation in severe emphysema but may overestimate dynamic hyperinflation possibly due to a higher breathing frequency.




## Introduction

In patients with emphysema, reduced elastic recoil of the lungs and increased airway resistance lead to static hyperinflation, *i.e.* an increased end expiratory lung volume. During exercise, due to a higher breathing frequency, the end expiratory lung volume may further increase at the expense of the inspiratory capacity (IC). This so-called dynamic hyperinflation contributes to dyspnea, reduced exercise tolerance and reduced quality of life [8]. There are various techniques to measure dynamic hyperinflation. Measuring the reduction in IC during cardiopulmonary exercise testing (CPET) is most commonly used and considered to be the reference standard [274]. Reduction in IC can also be measured with a metronome or manually paced tachypnea test (MPT), where the patient is instructed to breath with a high frequency for a set amount of time, or with a 6-min walk test (6-MWT) [265, 275]. Bronchoscopic lung volume reduction with endobronchial coils is a guideline treatment for selected patients with severe static hyperinflation and emphysema [1]. Coil treatment can lead to an improvement in static hyperinflation, exercise tolerance, and health status [37, 68]. For this study, we aimed to compare dynamic hyperinflation measured by CPET, 6-MWT, and MPT in patients with very severe emphysema who were treated with endobronchial coils. More specifically, we wanted to assess the accuracy and agreement of measuring dynamic hyperinflation with the MPT and 6-MWT compared to CPET. Additionally, we investigated whether dynamic hyperinfation changed after treatment with endobronchial coils.

## Methods

This single-center prospective study included patients with severe emphysema and hyperinflation who participated in an open-label trial investigating endobronchial coil treatment which was approved by the local ethics committee (NCT02179125). All patients provided written informed consent. Patients were included between September 2015 and November 2017. The coil treatment was performed during two separate bronchoscopic procedures under fluoroscopy while the patient was under general anesthesia. During each bronchoscopy, 9 to 13 nitinol coils were placed in one (usually upper) lobe. After 6 weeks, the second target lobe was treated during a second bronchoscopy, unless there were complications of the first treatment, in which case the second procedure was postponed or canceled. All measurements were performed at baseline and three months post-treatment. Post-bronchodilator spirometry, body plethysmography, and diffusing capacity were measured according to ATS/ERS guidelines [251, 253]. The CPET (an incremental cycle-ergometer test) and 6-MWT were performed according to current guidelines [254, 274]. For both tests, IC was measured with the use of a pneumotachograph beforehand (the mean of three reproducible measurements, defined as < 150 ml and/or < 5% between measurements) and 30 s after maximal exercise (mean of two measurements). IC was measured in a semi-recumbent position for the CPET and standing upright for the 6-MWT. The protocol for measuring dynamic hyperinflation with MPT was described in an earlier publication [265]. In short, after measurement of the baseline IC, patients were asked to breathe 40 times/minute for one minute, after which the IC was immediately measured again. This measurement was repeated three times. Dynamic hyperinflation was calculated by subtracting the IC post- test from the IC pre-test.



**Table 1** | Baseline and follow up outcomes for manually paced tachypnea test (MPT), cardio pulmonary exercise test (CPET) and 6-min walk test (6MWT)

| | Baseline | Follow up | p-value |
|---|---|---|---|
| **CPET** | | | |
| Dynamic hyperinflation (ml) | -740 (-1530 to -170) | -750 (-1300 to -320) | 0.93 |
| Breathing frequency (x/min) at maximum workload | 28 (16-55) | 26 (15-38) | 0.017 |
| Tidal volumes (ml) at maximum workload | 840 (480-1310) | 1010 (630-1780) | 0.001 |
| Maximum workload (Watt) | 27 (3 to 51) | 33 (16 to 61) | 0.001 |
| $VO_2$ peak (ml/min) | 719 (508 to 1090) | 770 (546 to 1109) | 0.13 |
| **MPT** | | | |
| Dynamic hyperinflation (ml) | -900 (-1470 to -540) | -990 (-1690 to -540) | 0.017 |
| Breathing frequency (x/min) | 40 (39 to 42) | 40 (39 to 41) | 0.53 |
| Tidal volumes (ml) | 589 (390 to 895) | 680 (460 to 975) | <0.001 |
| **6MWT** | | | |
| Dynamic hyperinflation (ml) | -335 (-690 to +60) | -480 (-930 to -110) | 0.11 |
| Distance | 321 (172 to 469) | 362 (160 to 469) | 0.004 |

*$VO_2$ = oxygen uptake.*

## Results

Twenty-nine patients were included: 21 female; median age 63 (range 44 to 76) years; $FEV_1$ 25 (14 to 43)%pred; and RV 231 (176 to 322)%pred. Treatment with coils resulted in a change in $FEV_1$ of + 95 (− 5 to + 320) ml, RV -390 (− 1490 to + 10) ml, and 6 min walk distance + 28 (-7 to + 174) meters (all $p \leq 0.001$, Wilcoxon Signed Rank test). At the baseline CPET, the median workload was 27 (3 to 51) Watt, with a peak $VO_2$ of 10.0 (7.7 to 15.4) ml/min/ kg. In post-treatment, there was a clinically relevant change in workload of + 7 (− 5 to + 16) Watt ($p<0.001$) [259], with no significant change in peak $VO_2$ (+ 0.2 (− 2.2 to + 2.9)). At baseline, dynamic hyperinflation was − 740 (− 1530 to − 170) ml, − 900 (− 1470 to − 540) ml and − 335 (− 690 to + 60) ml measured with CPET, MPT, and 6-MWT, respectively (Table 1). These differences between baseline dynamic hyperinflation per test were statistically significant (all $p<0.01$). Three months after treatment, there was no significant change in dynamic hyperinflation measured with CPET (0 (− 750 to + 430) ml, $p$ 0.93), MPT (− 18 (− 550 to + 230) ml, $p$ 0.17), and 6-MWT (− 85 (− 510 to + 500) ml, $p$ 0.11). In post-treatment, there was a significant change in tidal volumes during maximum effort for CPET (+ 110 (− 10 to + 710) ml, $p$ 0.001) and average tidal volumes for MPT (+ 55 (− 55 to + 260) ml, $p<0.001$) (Table 1). There was a strong association between dynamic hyperinflation measured by CPET and MPT (rho 0.660, $p<0.001$), and a moderate association between CPET and the 6-MWT (rho 0.361, $p$ 0.024). Measurements of dynamic hyperinflation with CPET and MPT were plotted in a Bland–Altman plot (Figure 1). There was a mean difference of 202 ml (95% CI – 287 to + 690 ml) between dynamic hyperinflation measured by CPET and MPT.



## Discussion

In this single-center prospective study, dynamic hyperinflation was measured in patients with severe emphysema using cardiopulmonary exercise testing, a manually paced tachypnea test, and a 6-min walk test. There was a strong significant association between dynamic hyperinflation measured by CPET and MPT. A Bland-Altman plot showed a moderate agreement between these two tests, with a mean difference of dynamic hyperinflation of 202 ml in favor of MPT. We found only a moderate association of 6-MWT with CPET. We previously demonstrated measurement of dynamic hyperinflation with MPT to be safe and feasible in patients with severe COPD [265]. In addition, this study demonstrates a strong association and moderate agreement between dynamic hyperinflation measurements with CPET and MPT.

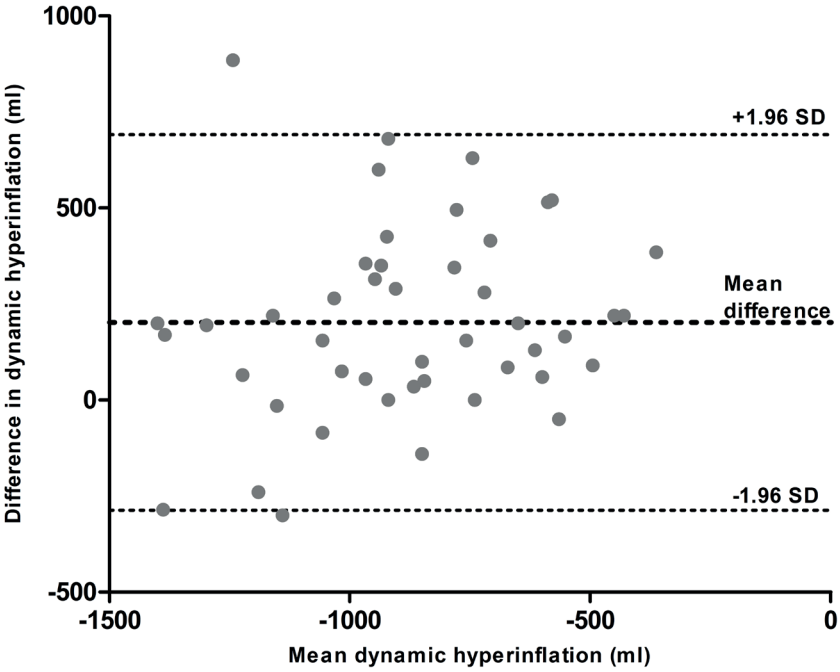


*Figure 1: A Bland–Altman plot of dynamic hyperinflation measured by cardiopulmonary exercise testing (CPET) and a manually paced tachypnea test (MPT).*

This strong association is in line with earlier studies [269, 276]. An advantage of MPT over CPET is that it is less costly and time consuming. A possible explanation for the 202 ml mean difference between dynamic hyperinflation measured with CPET and MPT in our study could be the difference in maximum breathing frequency (CPET: 26/min at maximum workload versus MPT: 40/min). MPT may, therefore, overestimate dynamic hyperinflation, since in real life, patients with severe emphysema may rarely reach a breathing frequency this high. Other possible explanations are a different interval between the end of the test and the IC measurement, a different posture (CPET: semi-recumbent versus MPT: sitting), and a different exercise state. However, earlier studies in patients with moderate to severe emphysema did not find a significant difference in dynamic hyperinflation between MPT and CPET [269, 276]. In this study, the 6-MWT appears to be a less suitable alternative for CPET to measure dynamic hyperinflation. During the study, the interval to IC measurement at the end of the test was often over the prespecified 30 s, mainly because of exhaustion of the patient who was then unable to correctly perform the IC maneuver after this short interval. This may explain in part why dynamic hyperinflation measured with the 6-MWT was significantly lower than CPET and MPT. There was no difference between dynamic hyperinflation before and after coil treatment in the current study. This is different from an earlier study we performed demonstrating an increase in dynamic hyperinflation measured

by MPT after bronchoscopic lung volume reduction with either coils or endobronchial valves [277]. The proposed underlying mechanism for this increase in dynamic hyperinflation is an increase in the inspiratory capacity because of the reduction in static hyperinflation, which leaves more room for dynamic hyperinflation to occur. In the current study, the improvement in static hyperinflation was less pronounced than in the earlier study (-390 versus -765 ml), which may in part explain why dynamic hyperinflation did not change. Furthermore, for the CPET and 6-MWT, there was a median increase in exercise capacity after treatment (+ 7 W and + 28 m, respectively), which means that the same amount of dynamic hyperinflation occurred at a later moment during exercise. However, this does not apply to the MPT, which is based on hyperventilation without exercise. In the current study, all patients had severe static hyperinflation and airflow obstruction and demonstrated an impaired exercise capacity on the basis of a ventilatory limitation during CPET. Both at baseline and follow-up, dynamic hyperinflation was demonstrated in all participating subjects. So even after coil treatment, dynamic hyperinflation is still likely to contribute to the reduced exercise tolerance. Therefore, one could argue that measuring the presence of dynamic hyperinflation in this patient category may not give additional information, since it is already highly likely that dynamic hyperinflation is present. However, to learn more about the quantity of dynamic hyperinflation and the effects of new treatments on dynamic hyperinflation, we believe it is still useful to perform measurements of dynamic hyperinflation in these patients. Study limitations are the relatively small sample size and that we investigated a selected group of emphysema patients with severe static hyperinflation, since these are prerequisites for bronchoscopic lung volume reduction treatments. Furthermore, there were some differences in the interval between the end of exercise or hyperventilation and the moment, the IC was measured between the three investigated tests, which could account for some of the differences in measured dynamic hyperinflation. In conclusion, we demonstrated that a manually paced tachypnea test is a suitable alternative to cardiopulmonary exercise testing to measure dynamic hyperinflation in patients with severe emphysema, although it may slightly overestimate dynamic hyperinflation. The 6-min walk test was a less suitable substitute to cardiopulmonary exercise testing for the measurement of dynamic hyperinflation. Furthermore, we measured no change in dynamic hyperinflation after treatment with endobronchial coils.



**Author's Contributions:** MD was responsible for data analysis, interpretation, and preparing the first draft of the manuscript. JH was responsible for the study design, recruiting participants, and data interpretation. SA was responsible for data acquisition. NH was responsible for the study design and recruiting participants. KK was responsible for the study design and recruiting participants. DS was responsible for the study design, recruiting participants, and supervision of the preparation of the manuscript. All authors were responsible for revising the manuscript.

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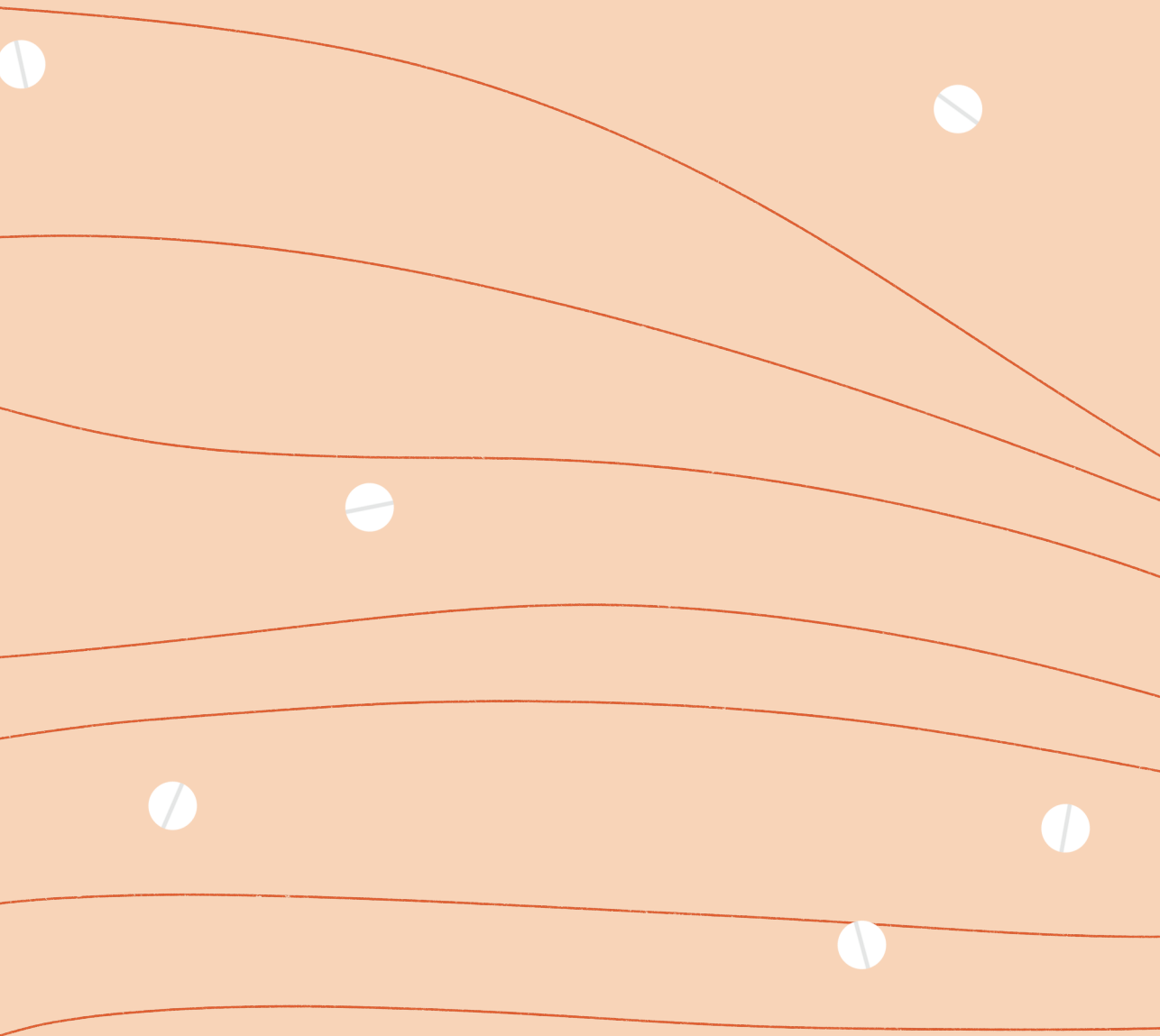
**Data Availability:** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Conflict of interest:** MD, JH, SA, NH, and KK have no real or perceived competing interests. DS reports grants and non-financial support from PneumRx/BTG, outside the submitted work.



CHAPTER 7

# First in human experience of the performance of the new 5.5-LP Size Zephyr endobronchial valve

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## Abstract

**Introduction:** Bronchoscopic lung volume reduction using endobronchial valves is a guideline treatment for patients with advanced emphysema. To achieve volume reduction, it is crucial that there is absence of collateral ventilation and a complete occlusion of the target lobe. While three EBV sizes (4.0;4.0-LP;5.5) are currently available to accommodate all airway sizes, local anatomical variations sometimes warrant a valve with a wide diameter but shorter length. To address this, a new 'low profile' 5.5-LP EBV has been introduced.

**Objective:** In this study we evaluated the feasibility, safety, and efficacy of this new 5.5-LP EBV.

**Method:** This was a single-center, prospective, open label study. Patients were included if eligible for valve treatment with a local anatomy suitable to place at least one 5.5-LP EBV. Feasibility of placement of the 5.5-LP EBV was reported. Safety, CT parameters, pulmonary function tests, and St. George's Respiratory Questionnaire (SGRQ) were assessed at baseline and 6 weeks after treatment.

**Results:** We included 30 patients with severe chronic obstructive pulmonary disease ($FEV_1$ 29±10%; RV 242±46%; and SGRQ 56±11 points). Besides the regular EBV sizes, a median of 1 (1 to 3) of the new 5.5-LP EBV was placed. No valve adjustment was needed during the initial procedure. A single asymptomatic small pneumothorax was observed in 1 patient. In 4 patients, a revision bronchoscopy was performed due to lack of clinical benefit. In 1 patient, this was related to a dislocation of the 5.5LP EBV. Clinically relevant and statistically significant improvements were seen in target lobar volume reduction -1554 ml, $FEV_1$ +39%, RV -960 ml, and SGRQ -18 points.

**Conclusion:** In this first in human study, the 5.5-LP EBV could be placed into wide segments with a shorter landing length without unexpected complications and with good efficacy outcomes.




## Introduction

Bronchoscopic lung volume reduction using one-way endobronchial valves (EBV; Zephyr; Pulmonx Corporation, CA, USA) is a guideline treatment for patients with advanced emphysema [1] and can lead to improvement in airflow obstruction, hyperinflation, exercise tolerance, physical activity [278], and quality of life [32-35, 67]. To achieve the desired volume reduction, it is crucial that there is proven absence of collateral ventilation and a complete occlusion with valves of the treatment target lobe [26]. The EBV is a nitinol self-expandable retainer with a silicone coating and valve mechanism which is bronchoscopically delivered to the (sub)segments of the target lobe [31]. Multiple valves are required to fully occlude the entire target lobe. Until recently, the EBV was available in 3 different sizes. The available sizes 4.0 EBV and 4.0-LP EBV are to be placed in bronchial lumens ranging

from 4.0 to 7.0 mm in diameter, with the sealing length of the valve of the 4.0-LP EBV being 25% shorter in length than the 4.0 EBV to accommodate shorter airway lengths. The 5.5 EBV is to be placed in bronchial lumens ranging from 5.5 to 8.5 mm in diameter and with a necessary sealing length of 8.0 mm. These 3 valve designs accommodate most airway anatomical variations. However, especially in the apical segments (both B1 and B6), a 5.5 EBV diameter range but with a shorter sealing length than 8.0 mm is sometimes needed and might facilitate easier procedures (see Figure 1 for available Zephyr® EBV). To address this need, a new "low profile" 5.5-LP EBV (sealing length 5.8 mm instead of the "regular" 8 mm length; diameter range 5.5–8.5 mm) has been introduced to accommodate shorter airway lengths in the targeted bronchial segment. While the sizes 4.0 EBV, 4.0-LP EBV, and 5.5 EBV have been available on the European market for many years, the 5.5-LP EBV has been introduced in September 2018 (see Figure 1 for available Zephyr® EBV). In this study, we tested the procedural performance of the new 5.5-LP EBV for the first time.

## Methods

This was a single-center, prospective, open-label study. We included patients with chronic obstructive pulmonary disease (COPD) and severe emphysema who were scheduled for EBV treatment and who received at least one new "low profile" 5.5-LP EBV. All patients in this study provided written consent, were treated in our hospital, and were registered in a national treatment registry (BREATH-NL: NCT02815683).



### *EBV Treatment*

EBV treatment was performed using a flexible therapeutic bronchoscope under general anesthesia as described before [31]. Prior to valve placement, the Chartis assessment was performed to determine collateral ventilation in the target lobe. Patients with absence of collateral ventilation and with a local anatomy suitable to place at least one 5.5-LP EBV to achieve complete occlusion of the target lobe were included in this study. Lobar occlusion was performed in a single sequence, and the valves were (sub)segmentally placed.

### *Follow-Up*

The feasibility of initial placement of the 5.5-LP EBV was reported. Safety was monitored. High-resolution CT, post bronchodilator pulmonary function tests, and SGRQ were assessed at baseline and 6 weeks after EBV treatment. Quantitative CT analysis was performed using Thirona's Lung Quantification (Thirona, Nijmegen, The Netherlands) on the baseline CT scan and the 6-week follow-up scan. Repeat bronchoscopy was performed if the patient did not experience clinical benefit at the 45-day follow-up visit and if the CT scan suggested a possible valve dislocation.

*Statistical Analysis*

Data are shown as median values (minimum to maximum) or as mean ± SD. The Wilcoxon signed rank test was used to compare results before and 6 weeks after EBV treatment. IBM SPSS statistics 23 (IBM, New York, NY, USA) was employed for statistical analysis.

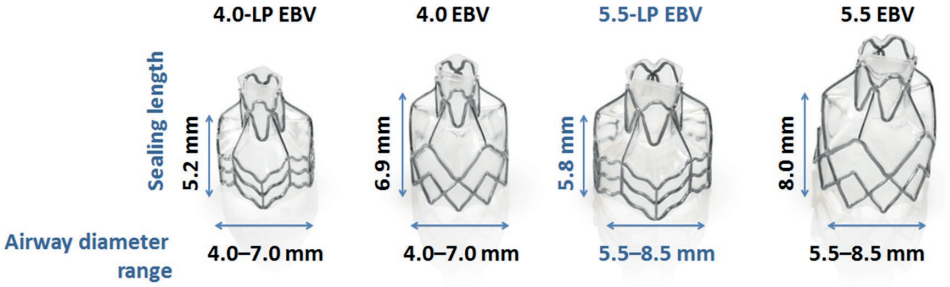


*Figure 1: Available Zephyr® endobronchial valves.*

## Results

From September 2018 to May 2019, thirty COPD patients with severe emphysema treated with regular EBVs and at least one 5.5-LP EBV were included in this analysis. See table 1 for demographics and baseline characteristics.

*EBV Treatment*

A median of 4 valves (range 2–6) were placed per patient, with a median of 1 (range 1–3) of the new 5.5-LP EBVs. In these 30 patients, a total of 41 new 5.5-LP EBVs were placed without additional valve adjustments or periprocedural replacements during the procedure. Procedural information is provided in Table 2.

**Table 1** | Demographics and baseline characteristics

| **Demographics and baseline characteristics** | **n=30** |
|---|---|
| Age, years | 61 ± 8 |
| Female/Male | 21 / 9 |
| BMI, kg/m² | 24 ±4 |
| $FEV_1$, % predicted | 29 ± 10 |
| FVC, % predicted | 71 ± 14 |
| $FEV_1$/ FVC % | 32 ± 8 |
| TLC, % predicted | 140 ± 14 |
| RV, % predicted | 242 ± 46 |
| RV/TLC, % | 63 ± 6 |
| $DL_{CO}$, % predicted | 32 ± 10 |
| SGRQ total score, points | 56 ± 11 |
| Target lobe volume, ml | 2042 ± 679 |
| Target lobe voxel density < -950HU, % | 52 ± 11 |

*Data are shown as mean ± standard deviation. BMI=Body Mass Index, $FEV_1$=Forced expiratory flow in 1-second, FVC=Forced Vital Capacity, TLC=Total Lung Capacity, RV=Residual Volume, $DL_{CO}$ = Carbon monoxide diffusing capacity, SGRQ=Saint George's Respiratory Questionnaire.*

*Efficacy*

Six weeks (50 ± 13 days) after EBV treatment, there was significant ($p$<0.001) clinically relevant improvement with respect to baseline levels regarding target lobar volume reduction, residual volume (RV), forced expiratory volume in 1 s ($FEV_1$), and SGRQ score. The median relative change in target lobar volume reduction on CT scan was –100% (range from –100 to –27%), in $FEV_1$ +285 mL (range from +70 to +870 mL), in RV –22% (range from –46 to +16%), and absolute median change in the SGRQ total score was –18 points (range from –38 to +12 points). See Figure 2 for effectiveness outcomes and responder rates.

*Revision Bronchoscopy*

At the 6-week follow-up visit, 4 patients did not have clinical benefit, and therefore a revision bronchoscopy was performed. In 1 patient, the lack of effect was related to dislocation of a 5.5-LP EBV. This patient had a clinically relevant lung volume reduction (RV was reduced by 870 mL) 3 months after revision bronchoscopy. See Table 3 for reasons for revision bronchoscopy.

**Table 2** I Endobronchial valve (EBV) procedure results

| **EBV Treatment** | **n=30** |
|---|---|
| **EBV placement duration — minutes** | 11 (5 -25) |
| **Target lobe for EBV treatment — no. (%)** | |
| Right Upper lobe | 2 (7%) |
| Right Upper + Middle lobe | 4 (13%) |
| Right Lower lobe | 2 (7%) |
| Left Upper lobe | 4 (13%) |
| Left Lower lobe | 18 (60%) |
| **EBV placed per patient — median no. (range)** | 4 (2-6) |
| EBV size 4.0 | 1 (0-3) |
| EBV size 4.0-LP | 0 (0-2) |
| EBV size 5.5 | 1 (0-3) |
| EBV size 5.5-LP | 1 (1-3) |
| **Segments treated with 5.5-LP EBV** | 5.5-LP EBV placed (n=41) |
| RB1 | 3 |
| RB2 | 2 |
| RB 3 | 1 |
| RB4/5 | 1 |
| RB6 | 3 |
| RB9/10 | 2 |
| LB1/2 | 1 |
| LB3 | 4 |
| LB6 | 14 |
| LB8 | 4 |
| LB9 | 3 |
| LB10 | 2 |
| LB8/9/10 | 1 |

**Table 3** | Reasons for revision bronchoscopy (n=4)

| | Related to 5.5- LP EBV | Segment | Reason for Revision Bronchoscopy |
|---|---|---|---|
| **Patient #1** | No | RB 4/5 | RUL was initially treated, in a 2nd procedure<br>RML was also treated with a 5.5 EBV |
| **Patient #6** | No | LB9 + LB10 | LB9 | One 5.5 EBV did not seem to close properly and was replaced by a 5.5 EBV<br>LB10 | One 5.5 EBV appeared to be slightly loose and was replaced by 3 valves (1 x4.0 EBV and 2x 4.0-LP EBV) |
| **Patient #11** | No | LB4/5 | LB4/5 | One 5.5 EBV appeared to be slightly loose and was replaced by 2x 4.0-LP EBV |
| **Patient #15** | Yes | RB1 | RB1 | 5.5-LP EBV was slightly migrated into RB1b therefore no occlusion anymore of segment RB1, an additional 5.5-LP EBV was placed into RB1 |

*RUL: right upper lobe; RML: right middle lobe; EBV: Zephyr® endobronchial valve.*

### *Safety*

No adverse events occurred during the initial EBV treatment and during revision bronchoscopy. In 30 patients, 1 (3%) small non-symptomatic apical pneumothorax was observed 4 days after treatment which did not require chest tube drainage. No other adverse events occurred in this study.

7

## Discussion

This is the first study investigating the procedural performance of the new 5.5-LP Zephyr EBV to bronchoscopically achieve lobar occlusion in patients with advanced emphysema and proven absence of collateral ventilation measured with Chartis. We found that placement of this new size valve is feasible. During the 30 initial valve placement procedures, using 41 new EBVs, no valve adjustments, replacements, or repositioning was required. In this study, the 5.5-LP valve was predominantly placed in the apical segments (LB6) due to a shorter length of the (sub)segment; however, it appeared that all segments allowed an easier treatment using this new valve design (Table 2). Placing a "regular 5.5 EBV" at these positions would have been suboptimal due to a too short "landing zone (length)"; alternatively, the 5.5-LP EBV-treated positions could have been treated using 2, 3, or even 4 smaller valves instead. We were able to successfully place the new 5.5-LP EBV in all segments where needed and together with the additional valves placed to achieve a successful lobar occlusion of the target lobe. Total lobar occlusion of the treatment target lobe was achieved in all patients resulting in a large (>1,554 mL) target lobe volume reduction exceeding by far the minimal clinically important difference [279].

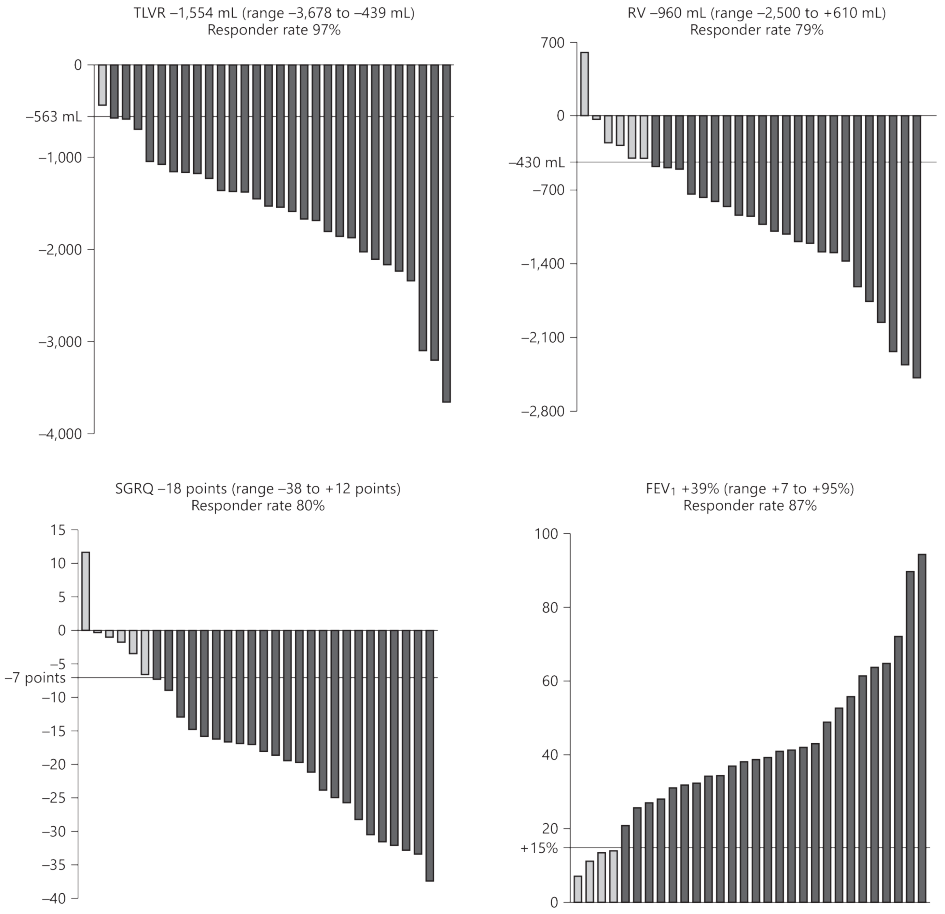


*Figure 2: Effectiveness outcomes and responder rates. Effectiveness outcomes in absolute change (TLVR, RV, and SGRQ) and in relative change ($FEV_1$) from baseline to follow-up 6 weeks after EBV placement. Data are shown as median values (minimum to maximum). All p<0.001. Wilcoxon signed rank test was used to calculate differences. Minimal clinically important difference (MCID) for TLVR was ≥563 mL reduction [279]; relevant change for $FEV_1$ ≥15% improvement; MCID for RV ≥430 mL reduction [257]; and MCID for SGRQ ≥7 points reduction [260]. It was not possible to obtain reliable body plethysmography measurement in 1 patient, with a TLVR on CT scan of –1,372 mL 6 weeks after EBV treatment.*

Remarkably, despite this significant lung volume reduction, we only observed a single non-symptomatic small pneumothorax (rate of 3.3% in n=30 patients treated). This rate is considerably lower than the rates reported in recent randomized controlled trials of the Zephyr EBV [32-34]. It is rather speculative why this rate is so low, while the outcome is optimal in this patient group. First, the majority (67%) was treated in the lower lobes, where in general a lower rate of pneumothoraxes occur compared to upper lobes. Second, we extubated the patients while they are still deeply sedated with strong cough suppression

for the first hour after treatment (intravenous lidocaine and opiates). Our patients are actively mobilized the morning after the procedure and discharged after at least 3 days of clinical observation. A limitation of this study is the short follow-up period of 6 weeks after treatment, which may not be sufficient to evaluate any late valve migrations. Our experience from previous studies [32-34] shows that approximately 10% valve migrations occur in the first 12 months after initial EBV treatment. Therefore, a longer follow-up is needed to evaluate the occurrence of migration of the 5.5-LP EBV.

## Conclusion

In this first in human study, the Zephyr 5.5-LP EBV is shown to be a viable option for placement in segments of wider diameter but shorter landing space. Total occlusion of the EBV treatment target lobe was successful in all patients. No unexpected adverse events occurred. Six weeks after EBV treatment, there was clinically relevant improvement in target lobar volume reduction on CT scan and in lung function outcomes. Long-term follow-up is needed to evaluate sustained effects.

**Statement of ethics:** All patients in this study provided written consent, were treated in our hospital; and were registered in a national treatment registry (BREATH-NL: NCT02815683). According to the ethics committee of our hospital; this study did not fall within the scope of the WMO (Dutch Medical Research with Human Subjects Law) and therefore formal approval was not needed.



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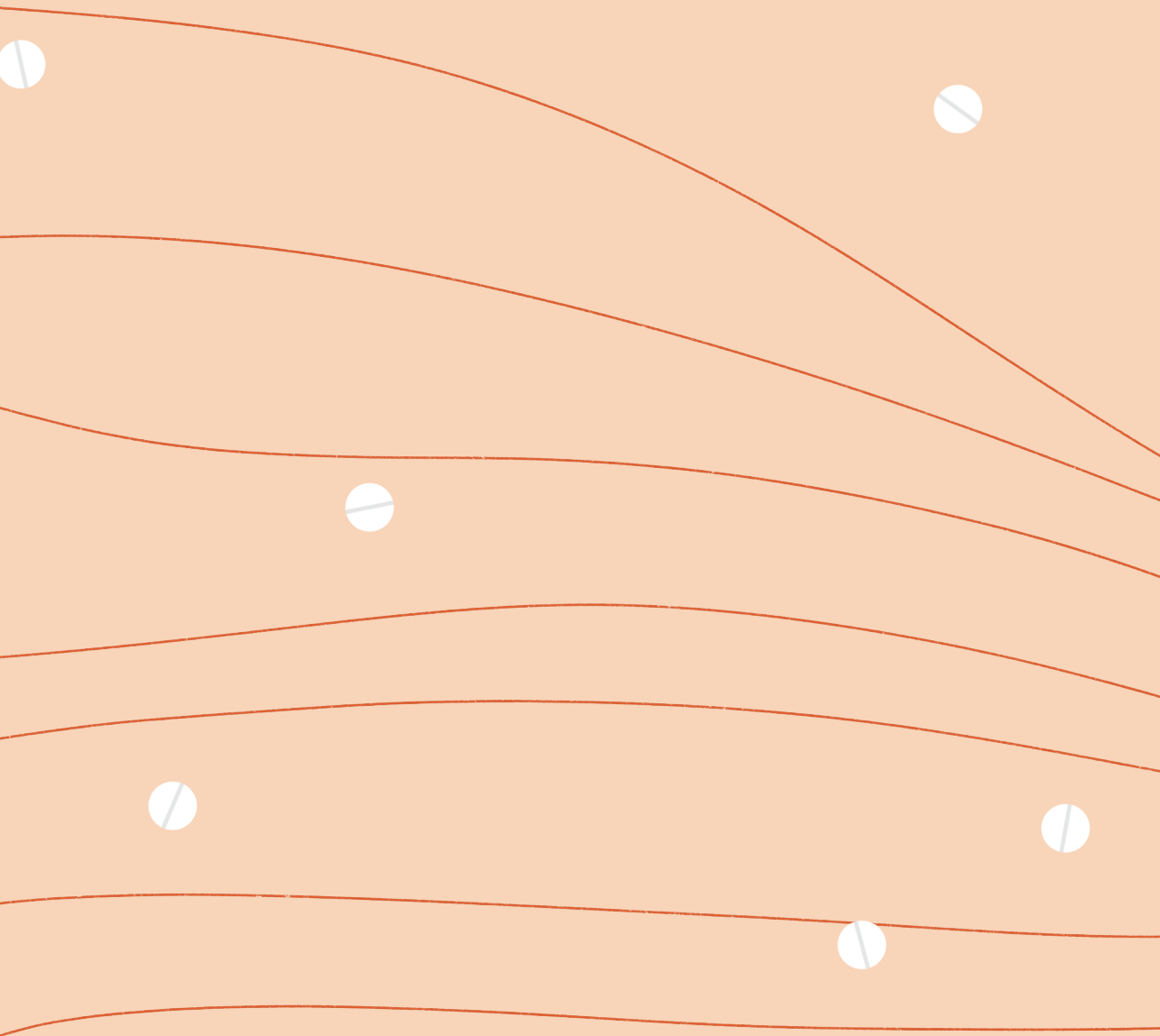
**Author contributions:** All authors had complete access to the data, and reviewed and approved the manuscript.



CHAPTER 8

# Expert statement: Pneumothorax associated with one-way valve therapy for emphysema: 2020 update

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*Adapted from Respiration. 2021;100(10):969-978*

## Abstract

For selected patients with advanced emphysema, bronchoscopic lung volume reduction with one-way valves can lead to clinically relevant improvements of airflow obstruction, hyperinflation, exercise capacity, and quality of life. The most common complication of this procedure is pneumothorax with a prevalence of up to ±34% of the treated patients. Patients who develop a pneumothorax also experience meaningful clinical benefits once the pneumothorax is resolved. Timely resolution of a post-valve treatment pneumothorax requires skilled and adequate pneumothorax management. This expert panel statement is an updated recommendation of the 2014 statement developed to help guide pneumothorax management after valve placement. Additionally, mechanisms for pneumothorax development, risk assessment, prevention of pneumothorax, and outcomes after pneumothorax are addressed. This recommendation is based on a combination of the current scientific literature and expert opinion, which was obtained through a modified Delphi method.


## Introduction

For selected patients with advanced emphysema, bronchoscopic lung volume reduction (BLVR) with one-way valves can lead to clinically relevant improvements of airflow obstruction, hyperinflation, exercise capacity, and quality of life [26, 280, 281]. Since 2019, BLVR with valves is acknowledged in the COPD GOLD guidelines with evidence grade “A” as a treatment option for patients with severe hyperinflation and severe emphysema and no collateral ventilation between the target lobe and ipsilateral lobe(s) [1]. The inclusion of BLVR treatment with valves in global treatment guidelines and increasing coverage by medical insurance in an increasing number of countries have resulted in a sharp increase in the number of BLVR valve procedures worldwide [280, 282]. With an increasing number of procedures worldwide, there will also be an increase in the absolute number of adverse events related to BLVR procedures with valves. The most common complication associated with valve procedures is a pneumothorax, which occurs in 4.2–34.4% of treated patients [33, 283]. This consensus statement provides an updated recommendation of the in 2014 published expert statement on pneumothorax associated with endoscopic valve therapy for emphysema [284] developed by an expert panel to help guide pneumothorax management after valve placement. Additionally, mechanisms for pneumothorax development, risk assessment, prevention of pneumothorax, and outcomes after pneumothorax are discussed.

## Methods

For this expert statement we reviewed the current scientific literature. However, for many of the topics discussed in his report there is no or inconclusive scientific evidence. To achieve expert consensus on these topics we performed a modified Delphi method [285], with a panel of 9 experts with extensive experience in BLVR with valves (median number

of valve procedures performed was >300 [range minimum 70–maximum 1,000]). Themes of the questionnaires were: risk assessment, prevention, diagnosis and treatment of pneumothorax after valve placement, and patient education. Two rounds were held given the prespecified criteria: 8/9 experts completed the first round, and 9/9 of the invited experts completed the second round. An extensive description of the modified Delphi procedure, the questionnaires and outcomes can be found in the online supplementary material. Furthermore, for each statement on consensus between experts in this article there is a reference to the relevant question and round in the online supplementary material. For example, "Finally, there was consensus regarding homogeneous emphysema distribution and a fast development of atelectasis after valve placement as risk factors [Q1,R2]" (Q = question, R = round).

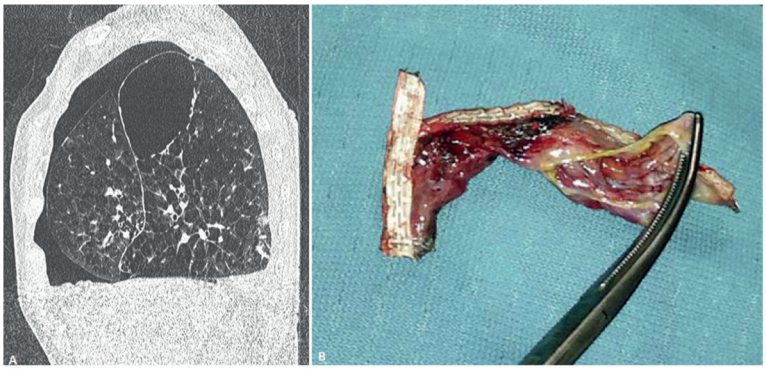

*Figure 1: a Pneumothorax and large bulla in the right lower lobe after valve treatment of the right upper lobe. b Example of VATS-resected lung tissue with ruptured bullae after valve treatment that caused a persistent significant air leak.*



### *Brief overview of valve procedure*

Patients with severe emphysema, severe static hyperinflation (residual volume [RV] >175%pred in heterogeneous emphysema, RV >200%pred in homogenous emphysema) and no collateral ventilation between the target lobe and ipsilateral lobe(s) are eligible for valve treatment [31, 36]. Contraindications are severe gas exchange impairment, severe airway pathology, frequent infectious exacerbations, and/or important cardiopulmonary comorbidity (*e.g.*, suspicious pulmonary nodules, pulmonary fibrosis, and severe heart failure) [31, 280].

The preferred target lobe is the lobe with the most diseased lung tissue. In case of more than one potential target lobe, nuclear scanning can help identify the lobe with the least perfusion. The degree of heterogeneity should also be taken into consideration, especially as treating a lobe where the ipsilateral lobe is better preserved has more favorable outcomes. Collateral ventilation can be assessed with quantitative CT analysis and/or measured during bronchoscopy with the Chartis® System (Chartis Pulmonary Assessment System, Pulmonx Corporation, Redwood City, CA, USA). The procedure for valve treatment

is preferably performed under general anesthesia using flexible or rigid intubation. An alternative option is moderate to deep conscious sedation with spontaneous breathing. During bronchoscopy each airway of the target lobe should be totally occluded with one-way valves to prevent airflow into the treated lobe. Depending on the anatomy and airway sizes of the treatment lobe the valves are placed at the segmental and/or subsegmental level. Additional information on the optimal performance of valve treatment can be found in the best practice recommendations by Slebos *et al.* [31].

*Mechanisms of pneumothorax after valve placement*

The atelectasis or volume loss that occurs in the target lobe following volume reduction allows the untreated ipsilateral lobe to expand to occupy the newly created space in the thoracic cavity. Brown *et al.* [286] showed that a part of the volume reduction in the target lobe is indeed redistributed to the ipsilateral lobe, with only a small portion redistributed to the contralateral lung. The expansion of the ipsilateral non-targeted lobe, which can be rapid and substantial, may in some cases exceed its limits of plasticity creating a bronchoalveolar fistula resulting in a pneumothorax. Rupture of blebs, bullae, and fragile lung tissue in the ipsilateral non-treated lobe are believed to be important contributing causes to a pneumothorax (Figure 1) [287]. Another mechanism could be parenchymal rupture due to pre-existing pleural adhesion(s) as the lobe volumes shift (Figure 2). A pneumothorax that results in a bronchoalveolar fistula has the potential to progress and precipitate clinical deterioration over a short amount of time if not treated by chest tube insertion. Another mechanism of pneumothorax is a pneumothorax ex vacuo [288]. In this condition, the lobar collapse results in an increase in the negative intrapleural pressure surrounding the collapsed lobe (Figure 3). As a result, gas originating from the ambient tissues and blood are drawn into the pleural space surrounding the collapsed lobe while the seal between the visceral and parietal pleura of the adjacent lobe or lobes remains intact [289]. No bronchoalveolar fistula is present in these cases, and the pleural air is expected to resolve spontaneously over time without the need for chest tube insertion. Typically, these patients have little to no symptoms, or already experience the induced lung volume reduction benefit. An interlobar pneumothorax is an uncommon occurrence after valve treatment, and can be difficult to diagnose on chest X-ray [284]. Finally, a pneumothorax might theoretically also originate from the barotrauma response to the acute volume reduction in the treated lobe. In this instance, the absence of an air leak might be due to the valves closing the originating bronchi. These cases of pneumothorax are expected to be less extensive on X-ray, and patients report minimal or no complaints. A “wait-and- see” policy is potentially successful in these patients.



*Prevalence and outcome of pneumothorax after valve treatment*

The prevalence of pneumothorax in randomized controlled trials (RCTs) investigating treatment with valves was 4.2–34.4% in the treatment groups compared to 0–4% in the control groups (Table 1) [32-35, 65, 290-293]. For RCTs investigating endobronchial valves (Zephyr® EBV, Pulmonx Corporation, Redwood City, CA, USA) there was a clear increase

in the prevalence of pneumothorax in more recent trials [32, 34, 35] compared to earlier trials [65, 290, 291]: 17.6– 34.4% versus 4.2–8%. The most likely explanation for this is a better patient selection in the more recent trials where patients were only treated with endobronchial valves in the absence of collateral ventilation, which was measured during bronchoscopy with the Chartis System. The use of Chartis for optimal patient selection has led to a greater target lobe volume reduction, greater treatment effect, and subsequently more pneumothoraces (Table 1). Similarly, the relationship between atelectasis and post-interventional pneumothorax was demonstrated in a case series of patients with emphysema using the Spiration valve system (formally intrabronchial valve) (SVS, Spiration Inc./Olympus Respiratory America, Redmond, WA, USA) [294]. In this trial, where patient selection was based on QCT (to determine absence of collateral ventilation) and not all patients received a full lobar occlusion with valves, the overall incidence of pneumothorax during a 12-month period was 12.1%. However, analysis of those patients who underwent a complete lobar exclusion (only of the left upper lobe) revealed a pneumothorax rate of 29% [294]. In the more recent EMPROVE trial with the SVS, quantitative CT analysis was used to assess the risk of collateral ventilation [292]. In this study, the pneumothorax rate was 25.7% in 113 treated subjects, similar to pneumothorax rates in the trials using Chartis and EBVs.

The majority of pneumothoraces (up to 86%) occur within the first 3 days after treatment [33, 292, 295, 296]. In general, the outcome of pneumothorax after valve treatment is resolution of the pneumothorax and there are no long-term sequelae. However, prolonged air leak is common. For example, in one retrospective trial the air leak persisted for over a week in 68% of pneumothoraces [297]. Of 799 patients who were treated in 9 RCTs, a fatal pneumothorax occurred in 6 patients (0.75%), and represents 4.6% of all patients with a pneumothorax [32-35, 65, 290-293]. Post hoc analysis of the pneumothorax events in the LIBERATE Study revealed that if the treated lobe was not the most diseased lobe (*i.e.*, the second best target was chosen) and the emphysema destruction in the contralateral lung was >60% (measured at −910 Hounsfield Units), the patient would be at a higher risk of death or require removal of all valves [33]. Of note, of the 6 fatal pneumothoraces mentioned above, 4 were in patients who were not treated in the most diseased lung lobe and had emphysema destruction of >60% in the contralateral lung, one pneumothorax occurred in the contralateral lung and one tension pneumothorax occurred during the removal of valves.

“Real life” unpublished data from the University Medical Center in Groningen (BREATHE-NL Registry, NCT02815683) shows similar outcomes compared to the scientific literature. Of the patients treated between September 2016 and March 2020, the overall pneumothorax rate after valve treatment was 16%, with the number of patients requiring a chest tube being 12% of treated patients.

**Table 1** | Prevalence, treatment, and outcome of pneumothorax after bronchoscopic lung volume reduction with one-way valves.

| Trial | Type valve | Follow up (Months) | No of treated patients | Pneumothorax | | | | | Average TLVR (ml) | Complete atelectasis No (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Occurence | | Chest tube No (%) | Valve removal No (%) | Death from PTX No (%) | | |
| | | | | PTX No | Patients with PTX No (%) | | | | | |
| **Sciurba** [291] | Zephyr | 3 | 214 | 9 | 9 (4.2) | 6 | Unknown | 0 (0) | 378.4 | Unknown |
| **Herth** [290] | Zephyr | 3 | 111 | 5 | 5 (4.5) | 5 | unknown | 0 (0) | Unknown | 20 (18) |
| **Davey** [65] | Zephyr | 3 | 25 | 2 | 2 (8) | 2 | 0 | 1 (4) # | Unknown | 8 (32) |
| **Klooster** [32] | Zephyr | 6 | 34 | 6 | 6 (17.6) | 5 | 3 | 0 (0) | 1366 (28 to 3604) | Unknown |
| **Valipour** [35] | Zephyr | 3 | 43 | 12 | 11 (25.5) | 12 | 5 | 0 (0) | 1195±683 | Unknown |
| **Kemp** [34] | Zephyr | 6 | 65 | 20 | 19 (29.2) | 11 | 5 | 1 (1.5) $ | 1090±620 | Unknown |
| **Criner** [33] | Zephyr | 12 | 128 | 46 | 44 (34.4) | 38 | 12 | 3 (2.3) | 1030±680 | Unknown |
| **Li** [293] | SVS | 6 | 66 | 5 | 5 (7.6) | 5 | 0 | 0 (0) | 757 | Unknown |
| **Criner** [292] | SVS | 6 | 113 | 32 | 29 (25.6) | 12.4 | 11 | 1 (0.9) * | 974±736 | Unknown |

*Zephyr=Zephyr Endobronchial Valve, SVS=Spiration Valve System, Ptx=pneumothorax, TLVR=target lung volume reduction.*

*# Patient developed a cough and a decision was taken to remove the valves 49 days after they had been placed. At the time of removal, which was difficult, patient developed a tension pneumothorax with an ongoing significant air leak, in-hospital cardiac arrest.*

** Pneumothorax in the contralateral lung.*

*$: Cardiac arrest during hospitalization for a pneumothorax.*

A post hoc analysis of 3 prospective studies analyzing outcomes for patients who developed a pneumothorax after valve treatment demonstrated substantial reductions in the target lobar volume (65± 36%) at follow-up [297]. This is of particular clinical importance as patients with a >50% reduction in target lobar volume demonstrate clinically significant benefits in hyperinflation, exercise capacity, quality of life, and airflow obstruction [298]. A retrospective analysis of 70 patients with pneumothorax confirmed that a pneumothorax generally has no negative impact on the clinical status [299]. Furthermore, in another large retrospective analysis investigating long-term effects of valve treatment, the occurrence of a pneumothorax did not influence survival [300]. More recently, the LIBERATE trial demonstrated no differences in outcome for patients who did and did not develop a pneumothorax after valve treatment [33].

### *Predicting pneumothorax: risk assessment*

Since pneumothorax is a common adverse event following valve treatment, alertness for the occurrence of a pneumothorax after procedure should always be high. However, there are certain risk factors that are considered to increase the chance of a pneumothorax or a poor outcome of pneumothorax after procedure (*i.e.*, prolonged air leak or death; Table 2).

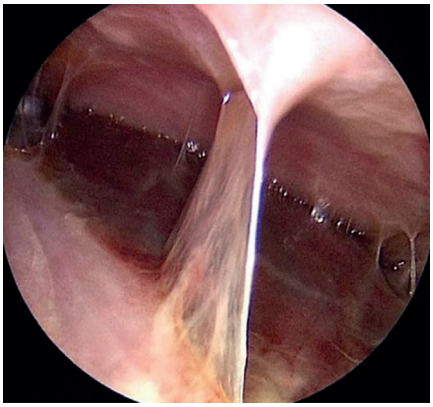

*Figure 2: Pleural adhesion as observed during VATS. VATS: video-assisted thoracoscopy.*

### *Pleural adhesions*

Pleural adhesions can be identified on a Chest CT scan as fibrotic bands with pleural involvement [301]. With respect to the presence of pleural adhesions and risk of pneumothorax, there is ambiguity in the literature. One retrospective study demonstrated an increased risk of pneumothorax in patients with a higher number or greater size of pleural adhesions [301], but in another retrospective study the presence of pleural adhesions was associated with a lower risk of pneumothorax [296]. In the large multicenter LIBERATE trial investigating Zephyr valves, the presence of pleural adhesions was not identified as a risk factor for pneumothorax [33]. Nevertheless, the expert panel does regard the presence of pleural adhesions (both number and size) as an important risk factor for pneumothorax after valve treatment, where adhesions in the untreated lobe are more likely to be contributing to the risk of developing a pneumothorax [Q1,R1].

*Emphysema phenotype*

The presence of paraseptal emphysema was identified as a risk factor for the development of a pneumothorax by the expert panel [Q1,R1]. The presence of blebs or paraseptal cysts did not have a significant predictive value for a pneumothorax in either the prospective LIBERATE trial or the retrospective analysis of Gompelmann *et al.* [33, 296]. Compared to centrilobular emphysema, panlobular emphysema was found to be protective in the study by Gompelmann *et al.* [296].

*Lobar volumes and emphysema destruction*

Gompelmann *et al.* [296] further identified a large difference in the volume of the target lobe versus the ipsilateral lobe(s), a high destruction score in the ipsilateral untreated lobe and a high baseline RV as factors increasing the risk of pneumothorax related to valve treatment. The volume difference between target and ipsilateral lobe(s) was also identified as a factor increasing the risk of pneumothorax by the expert panel [Q1,R1]. Finally, there was consensus regarding homogeneous emphysema distribution and a fast development of atelectasis after valve placement as risk factors [Q1,R2]. It has been hypothesized that the risk of pneumothorax following valve treatment is higher for an upper lobe treatment compared to treatment in a lower lobe. Two trials did demonstrate a non-significant trend toward more pneumothoraces when treating upper lobes as opposed to lower lobes [32, 302]. There was no consensus within the expert panel with respect to this risk factor [Q4,R1].

As mentioned above, post hoc analysis of data from the LIBERATE trial revealed that patients not treated in the most diseased lobe (treated in secondary lobe in contralateral side) and in whom the emphysema destruction score was >60% at −910 Hounsfield Units on chest CT, were at a higher risk of a complex pneumothorax (defined as leading to death or requiring valve removal) if one were to occur. The 3 patient deaths attributed to a pneumothorax event in this trial were later identified to be in this higher risk group [33].



**Table 2** | Possible risk factors for developing a pneumothorax after valve treatment and possible risk factors for a poor outcome of pneumothorax after valve treatment.

| **Possible risk factors for a pneumothorax after valve treatment:** | **Possible risk factors for a bad outcome in case of pneumothorax after valve treatment** |
|---|---|
| ✓ Significant pleural adhesions in target lung | ✓ Target lobe not the most destructed lobe |
| ✓ Significant paraseptal emphysema | ✓ High destruction score in the ipsilateral lobe(s) and contralateral lung |
| ✓ Large difference in volume of target lobe vs. ipsilateral lobe(s) | ✓ Pneumothorax in the best perfused lung |
| ✓ High emphysematous destruction score of ipsilateral non-treated lobes(s) | ✓ Very severe airflow obstruction ($FEV_1$ <15%) |
| ✓ Homogeneous emphysema distribution | ✓ Severely impaired diffusing capacity ($DL_{CO}$<20%) |
| ✓ Rapid onset of atelectasis | ✓ Severe chronic respiratory failure ($PaCO_2$ >55 mmHg, $PaO_2$ <45 mmHg) |

In the large multicenter NETT, lung volume reduction surgery was demonstrated to have a positive effect on lung function, exercise tolerance, and quality of life. However, during

the trial a high-risk patient category was identified who had a significantly higher 90-day mortality (28.6 vs. 5.2%). These were patients with an $FEV_1$ of below 20% of predicted and either a homogeneous emphysema distribution or diffusing capacity ($DL_{CO}$) below 20% of predicted [30]. Two retrospective trials investigated valve treatment in patients with an $FEV_1$ <20% and $DL_{CO}$<20%, respectively, and demonstrated no increased risk for pneumothorax or increased mortality [261, 303]. However, these were both small trials and there was consensus between the expert panel that both a very severe airflow obstruction and severely impaired diffusing capacity at baseline increase the risk of a poor outcome (*i.e.*, death or prolonged air leak) in case of pneumothorax post-valve treatment [Q2,R1]. Other factors identified by the expert panel that increase the risk of an unfavorable outcome in case of pneumothorax were high emphysema destruction scores in the ipsilateral nontarget lobe and contralateral lung, the development of a pneumothorax in the best perfused lung, and severely impaired gas exchange at baseline [Q2,R1; Q2,R2].

*Preventing and diagnosing pneumothorax during and after procedure*

Experts have no consensus about strategies during valve procedure in order to reduce pneumothorax risk [Q3,R1]. Some suggestions are adjusting ventilator settings (low frequency ventilation, long expiration time), avoid tracheal intubation, administration of cough suppressants (opioids, lidocaine, codeine), reducing procedure time, avoidance of suctioning after placement of the last valve and 24- to 72-h relative rest after procedure.

In a prospective analysis of patients treated with a new size Zephyr valve, Klooster *et al*. [304] found a very low pneumothorax rate (3%) despite a significant clinically relevant reduction in lung volume. The authors suggested that extubation of patients while they are deeply sedated with strong cough suppression for the first hour after treatment (intravenous lidocaine and opioids) and little to no mobilization until the morning after the procedure could be possible explanations for the low pneumothorax rate.



Staged placement of valves in the target lobe during 2 sequential bronchoscopy procedures has been reported to reduce pneumothorax rate while providing clinically relevant lung volume reduction effect. Two single center uncontrolled case series reported a pneumothorax rate of 4.5 and 5.2% with sequential valve placement [305, 306]. However, a staged placement of valves was not recommended by the expert panel [Q4,R1]. One argument for this could be that an additional bronchoscopy also increases risk of bronchoscopy-related complications [307]. Although the results from the case studies may appear encouraging, given the impact of changing the treatment strategy from 1 to 2 procedures, a solid RCT should be performed to give a conclusive answer.

Since the majority of pneumothoraces occurs in the first 3 days after valve treatment a hospital admission of at least 3 nights after the procedure is advised by the expert panel [Q6,R1]. Observation during hospitalization should include clinical examination, assessment of vital signs at least once daily, and instructing the patient to immediately refer any chest pain or increase in dyspnea [Q8,R1; Q5,R2]. It is further recommended that multiple chest

X-rays be taken during the hospital admission, with the first X-ray taken within a few hours after the procedure [Q9,R1]. In case of persisting (severe) chest pain, increased dyspnea, lower oxygen saturations, or the presence of a pneumothorax ex vacuo the expert panel advises prolonging the hospital admission [Q7,R1]. One retrospective analysis found significantly less pneumothoraces in 40 patients who were prescribed bed rest, and "as needed" codeine for the first 2 days after valve treatment compared to 32 patients with no restrictions on mobilization and no codeine (25 vs. 5%, $p$=0.02); there were no differences in clinical outcomes between the groups [308]. However, in this retrospective trial, the number of patients was limited, and hence, the expert panel has not recommended any restriction on mobilization during hospital admission [Q10,R1]. One important concern for prescribing restrictive mobilization during hospital admission may be the occurrence of a delayed pneumothorax post-hospital admission.

**Table 3** | Recommendations for optimal post valve treatment care in the ward based on consensus.

**Hospital admission for at least three nights**
- Prolong in case of (severe) chest pain, increased dyspnea, lower oxygen saturations or the presence of a pneumothorax ex vacuo

**High awareness of risk of pneumothorax**
- Training and education of medical staff
- Clear information on procedure in medical charts

**Multiple chest X-rays during admission**
**Emergency pneumothorax kit available on the ward #**
**Patient and caregiver education before discharge**
- Patient warning card

**# Recommended contents of pneumothorax emergency kit:**
- A chest tube (minimal size 10-14 French) and drainage system
- A needle for immediate needle decompression
- Materials for disinfecting the skin
- Materials for local anesthesia
- Surgical drapes
- Sterile gloves, a sterile gown/scrubs, scrub caps, surgical mask
- Materials for securing the chest drain (suture set, bandages and tape)
- Pigtail catheter

Patient and caregiver education before hospital discharge is important and should include information about symptoms of an acute pneumothorax (acute dyspnea and/or chest pain), need to seek immediate emergency care, the emergency number and what information to provide to medical personnel, what activities to avoid and for how long [Q14,R1]. However, there was no consensus between experts regarding the exact advice for patients with respect to household chores, physiotherapy, and air travel during the first weeks after treatment [Q11–13,R1]. This is probably in part because of differences in healthcare systems and whether travel between hospital and home involves transportation by air.

*Pneumothorax management*

Patients who are candidates for endoscopic valve therapy have severe emphysema with hyperinflation, impaired gas exchange, and exercise capacity. Thus, these patients are less likely to tolerate a pneumothorax than patients with a primary spontaneous pneumothorax. Skilled and adequate pneumothorax management is therefore essential in this patient population and every pneumothorax, in particular a tension pneumothorax, can be life threatening [294]. It is therefore recommended by the expert panel that all medical staff involved in the post-procedure care of these patients in an institution where valve treatments are performed are thoroughly educated in diagnosing a pneumothorax and pneumothorax management [Q16,R1; Q6,R2]. An emergency kit for treating pneumothoraces should be close at hand, at a minimum in the ward, but wherever possible, by the patient's bedside [Q15,R1]. The recommended contents of the emergency kit can be found in Table 3. The updated management recommendation (Figure 4), based on the consensus procedure by the expert panel, is intended to provide guidance for physicians dealing with these cases in clinical practice. By following these recommendations, traumatic scenarios, prolonged drainage, extended hospital stays, and/or surgery might be minimized in many cases.

Based on clinical signs and symptoms, the pneumothorax is classified as symptomatic or asymptomatic. If the pneumothorax is asymptomatic, clinical observation may be enough and a repeat X-ray is recommended. Patients with an asymptomatic pneumothorax can be discharged if the pneumothorax is stable or improving on the chest X-ray and they are clinically stable [Q4,R2]. If clinical symptoms deteriorate or the size of the pneumothorax is enlarging, immediate insertion of a chest drain is required.

For every symptomatic pneumothorax insertion of a chest drain is required [Q17,R1]. The minimal advised chest drain size is 10–14 French [Q20,R1]. If available, an electronic drain system is preferable to a water seal system, provided the air leak is not too high for the electronic drainage system [Q21,R1]. Suction is generally not advised to start with but is an option in case of a clinically unstable patient, severe subcutaneous ("surgical") emphysema or if the lung does not expand after one or more days of chest drainage [Q19,R1]. The chest drain can be removed when there has been no air leak for over 24 h and the pneumothorax is stable or improving on chest X-ray [Q11,R2]. Switching to a larger chest drain or placement of an additional chest tube should be considered in the following situations: If the patient is deteriorating, subcutaneous emphysema is increasing or there is a very high flow and the lung does not expand despite a functioning chest drain [Q22,R1]. Removal of one or 2 valves can be considered in case of a persistent high air leak (*i.e.*, >3 days) or if the patient clinically deteriorates [Q23,R1]. This is likely to return the target lobe to its (hyperinflated) pretreatment state and may promote pneumothorax healing by reestablishing pleural contact. The lack of full expansion and pleural sealing of the untreated lobe might however also be due to endobronchial mucus plugging requiring bronchoscopic suction. Replacement of valves can be considered after valve removal to manage a pneumothorax, but not within the first 5 weeks after the pneumothorax has resolved [Q25,R1]. There is no published data on

recurrence of pneumothorax after valve replacement. However, in 2 expert centers, the recurrence rate was 17 and 29%, respectively.

In cases with a persistent air leak, performing a CT scan can also be considered to guide treatment options and/or rule out aberrant chest tube placement [Q12,R2].

Additional treatment options for a prolonged air leak are surgery, use of a Heimlich valve or mechanical or chemical pleurodesis [Q27,R1]. The timing and choice of the therapeutic approach may largely depend on the patient's condition, patient preference, and the experience with and availability of these treatment options at the institution where the valve treatment was performed. In patients with severe heterogeneous emphysema, the surgical approach might be conducted with the intent of volume reduction, though high rates of cardiopulmonary morbidity, and mortality need to be taken into consideration [309].

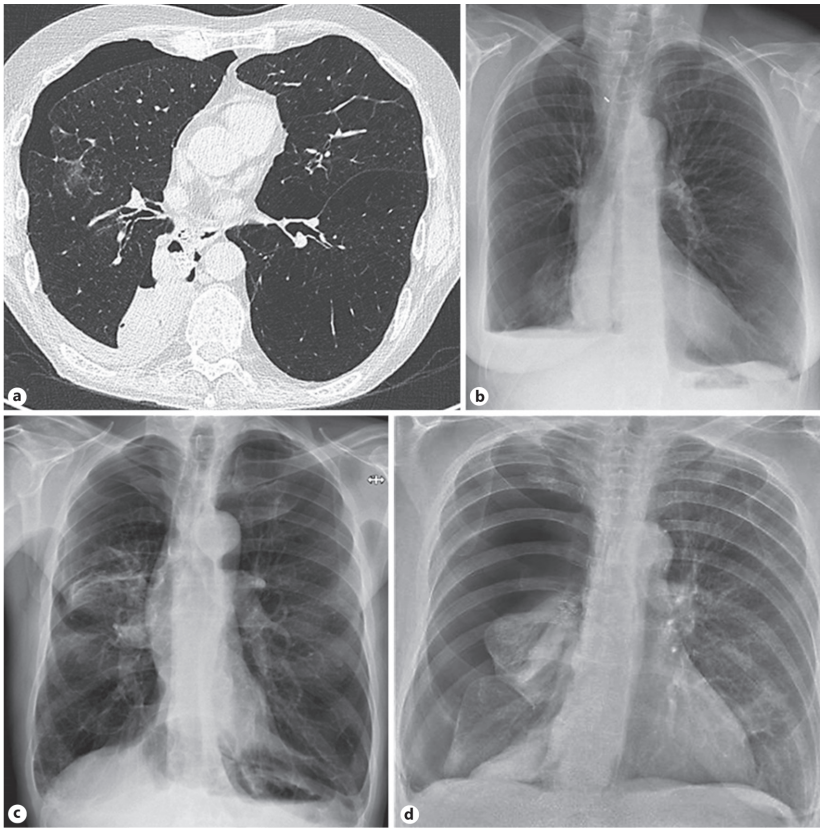


*Figure 3: a Pneumothorax ex vacuo on a chest CT scan after valve treatment in the left upper lobe. The patient received no intervention. The pneumothorax was asymptomatic and resolved within 4 weeks. b, c Pneumothorax ex vacuo on chest X-ray. d Complete pneumothorax for which acute intervention is needed.*

Most patients with a valve-associated pneumothorax however do not require surgical interventions and can be safely treated with a chest tube in the presence of a prolonged air leak. Discharge with a Heimlich valve can be considered, provided the patient is clinically stable, hospital care is nearby (<30 min) in case of drain dysfunction and the patient has been educated about drain care [Q8,R2; Q9,R2].

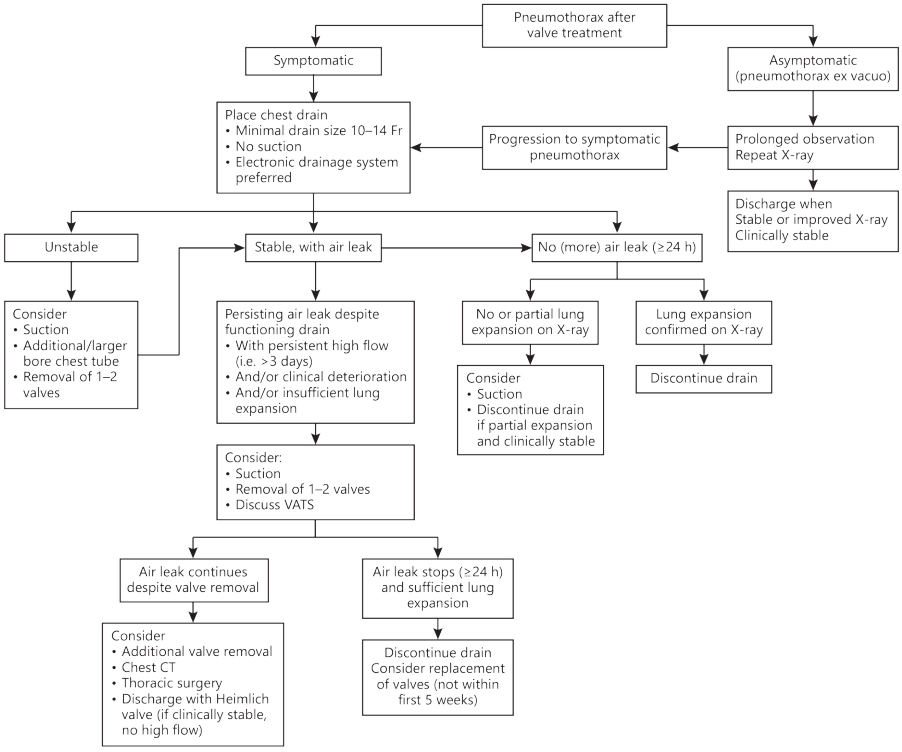


*Figure 4: Pneumothorax management recommendations. The recommended timelines in the proposed algorithm may differ individually depending on the patient's clinical status, the air leak volume, patient preference, and/or the local resources and expertise. VATS, video-assisted thoracic surgery.*

## Limitations

This consensus statement has limitations. The scientific literature related to pneumothorax occurrence after valve treatment largely consists of post hoc and retrospective analyses. This introduces an important selection bias and may also explain at least some of the discrepancies between the literature and expert opinion. For example, patients with large bullae on the chest CT are commonly excluded from participating in trials investigating valve treatment. Thus, the fact that clinical trials did not find an elevated pneumothorax risk in patients with paraseptal bullae or blebs could be influenced by selection bias. Furthermore,

the recommendations presented here are largely derived from clinical experience and a consensus of expert opinions, rather than scientific evidence or intervention studies. However, by introducing a modified Delphi method, we have aimed to take a more systemic approach to establish the expert opinion. Nevertheless, there is still a need for further prospective research into both baseline predictors of a pneumothorax and management strategies of pneumothorax. This may help optimize the risk-to-benefit ratio of patients undergoing valve therapy for lung volume reduction.

## Conclusion

The occurrence of a pneumothorax and its management should be considered routine clinical care when performing BLVR with valves in patients who have progressive disease, severely compromised lung tissue, and limited therapeutic options. With this in mind, the authors would like to propose a pragmatic management plan that attempts to guide physicians in daily practice. Given optimized patient selection, the risk-to-benefit ratio of a pneumothorax appears to be acceptable as many of these patients develop substantial improvements in functional outcomes after resolution of the pneumothorax.

## Future research questions

Is there an increased pneumothorax risk, when:

- There is fast development of an atelectasis after valve treatment?
- The Chartis measurement is CV-negative in a short amount of time?
- There is moderate paraseptal emphysema?

Can the risk of pneumothorax be lowered by?

- Performing a staged valve placement? Investigated in a randomized controlled trial
- Administering cough suppressants during or after procedure?

Does the use of point-of-care chest ultrasound have additional value in a timely diagnosis of pneumothorax after valve treatment?

Is there a place for prophylactic chest tube placement? For example, when there is a great imbalance between the treatment lobe and ipsilateral lobe(s)

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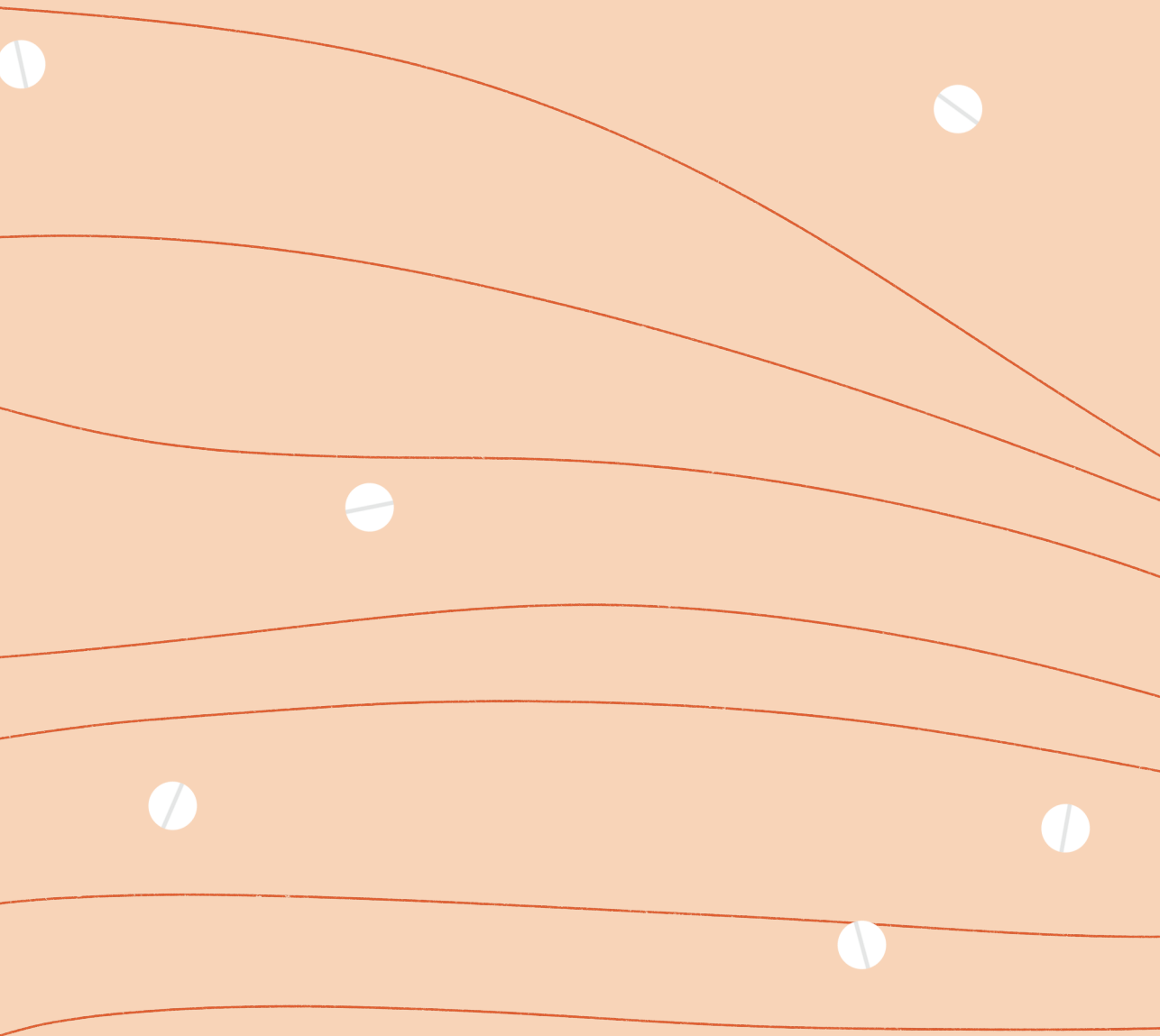
personal fees from BTG; grants, personal fees, nonfinancial support, and other from Olympus; grants and personal fees from Broncus; personal fees from EOLO; personal fees from NGM; grants and personal fees from Lungpacer; grants from Alung; grants and personal fees from Nuvaira; grants and personal fees from ResMed; grants and personal fees from Respironics; grants from Fisher Paykel; grants and personal fees from Patara; grants from Galapgos; personal fees from Amgen; personal fees from Medtronic Vascular; personal fees and nonfinancial support from Spiration; personal fees from Auris Health; personal fees from CSA Medical; personal fees from Novartis Pharma AG; nonfinancial support from Intuitive Surgical, Inc; personal fees from Regeneron Healthcare Solutions, Inc; and other from Philips Electronics North American Corp, outside the submitted work. D.G. has received travel and lecture fees from Olympus and PulmonX. F.H. has received consultancy and lecture fees from Olympus and PulmonX. D.K.H. has received consultancy fees from Olympus and PulmonX and is a consultant for Eolo. K.K. has received travel and lecture fees from PulmonX. J.W.H.K. has no financial disclosures or conflicts of interest relating to the current paper. H.G.O. has no financial disclosures or conflicts of interest. P.L.S. has received consultancy and lecture fees from Olympus and PulmonX. A.V. has received speaker fees from Olympus and PulmonX. D.S. is an investigator and advisor to PulmonX.

*Author contributions*

M.D. contributed to the development of the questionnaires, analysis of the outcomes, and the writing of the manuscript. R.S. contributed to the development of the questionnaires, was part of the expert panel, and contributed to the revision of the manuscript. G.J.C., D.G., F.J.F., D.K.H., H.G.O., P.L.S., and A.V. were part of the expert panel and contributed to the revisions of the manuscript. K.K. contributed to the writing of the manuscript. J.W.H.K. has expertise on the use of the Delphi method and contributed to the development of the modified Delphi method used for the current study. D.J.S. contributed to the development of the questionnaires and analysis of the outcomes, was part of the expert panel, and contributed to the writing of the manuscript.

Link to online supplementary material:



CHAPTER 9

# Opioids in patients with COPD and refractory dyspnea: literature review and design of a multicenter double blind study of low dosed morphine and fentanyl (MoreFoRCOPD)

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## Abstract

**Background:** Refractory dyspnea or breathlessness is a common symptom in patients with advanced Chronic Obstructive Pulmonary Disease (COPD), with a high negative impact on quality of life (QoL). Low dosed opioids have been investigated for refractory dyspnea in COPD and other life-limiting conditions, and some positive effects were demonstrated. However, upon first assessment of the literature, the quality of evidence in COPD seemed low or inconclusive, and focused mainly on morphine which may have more side effects than other opioids such as fentanyl. For the current publication we performed a systematic literature search. We searched for placebo-controlled randomized clinical trials investigating opioids for refractory dyspnea caused by COPD. We included trials reporting on dyspnea, health status and/or QoL. Three of fifteen trials demonstrated a significant positive effect of opioids on dyspnea. Only one of four trials reporting on QoL or health status, demonstrated a significant positive effect. Two-thirds of included trials investigated morphine. We found no placebo-controlled RCT on transdermal fentanyl. Subsequently, we hypothesized that both fentanyl and morphine provide a greater reduction of dyspnea than placebo, and that fentanyl has less side effects than morphine.

**Methods:** We describe the design of a robust, multi-center, double blind, double-dummy, cross-over, randomized, placebo-controlled clinical trial with three study arms investigating transdermal fentanyl 12 mcg/hr and morphine sustained-release 10 mg b.i.d. The primary endpoint is change in daily mean dyspnea sensation measured on a numeric rating scale. Secondary endpoints are change in daily worst dyspnea, QoL, anxiety, sleep quality, hypercapnia, side effects, patient preference, and continued opioid use. Sixty patients with severe stable COPD and refractory dyspnea ($FEV_1$<50%, mMRC≥3, on optimal standard therapy) will be included.

**Discussion:** Evidence for opioids for refractory dyspnea in COPD is not as robust as usually appreciated. We designed a study comparing both the more commonly used opioid morphine, and transdermal fentanyl to placebo. The cross-over design will help to get a better impression of patient preferences. We believe our study design to investigate both sustained-release morphine and transdermal fentanyl for refractory dyspnea will provide valuable information for better treatment of refractory dyspnea in COPD.




## Background

Refractory dyspnea or breathlessness is a common symptom in patients with advanced chronic obstructive pulmonary disease (COPD), with a prevalence of up to 94% in the last year of life [22, 310]. It is defined as persisting complaints of dyspnea despite optimal standard therapy including, but not limited to smoking cessation, education, inhaled bronchodilators and pulmonary physiotherapy [311]. Refractory dyspnea is known to severely impact quality of life and exercise tolerance, and to increase the risk of depression and anxiety [12]. As the

prevalence of COPD is expected to rise during the upcoming decades [1], it is likely that the number of patients with COPD suffering from refractory dyspnea will also continue to grow.

Advanced treatments such as non-invasive ventilation, bronchoscopic lung volume reduction and lung transplantation can improve dyspnea and quality of life in patients with advanced COPD [312]. But these treatments are only available for a proportion of patients with advanced COPD, due to strict eligibility criteria, high health-care costs and sometimes scarcity. Therefore, there is still a need for more widely available treatments of refractory dyspnea. In this context low dosed opioids have previously been investigated, and some positive effect was demonstrated [313-315]. However, whether the quality of the evidence is sufficient is still a topic of discussion. Furthermore, despite a positive advice on opioids in palliative care guidelines for COPD, prescription appears to be low in clinical practice [150, 316, 317].

We performed a systematic literature search with respect to opioids for refractory dyspnea in COPD, which we updated for the current publication to include all recent trials. We searched for placebo-controlled randomized clinical trials investigating any type of opioid prescribed for dyspnea reduction in COPD (at least 50% of participants). We included trials reporting on dyspnea, health status and/or quality of life. Additional details on the search strategy can be found in the online supplement, including a flow chart on the number of records identified, screened and included.

Table 1 shows an overview of the trials we identified as a result of our search strategy. In total, fifteen trials were included. A statistically significant positive effect on dyspnea of opioid versus placebo was demonstrated only in three studies [313, 314, 318]. Since the majority of these studies included a small number of patients, the lack of statistically significant results may in part be explained by a low statistical power to detect a treatment effect. This assumption is supported by a meta-analysis published by Ekström *et al.* in 2015, in which a positive effect on dyspnea was found for both systemically administered and nebulized opioids (analyses of combined data of 8 and 4 trials, respectively) [149]. Nevertheless, the three largest studies in our table, which all have been published more recently, demonstrated no significant change in dyspnea for sustained-release morphine and oxycodone [319-321]. While assessing this, it is important to note that in the studies of Currow *et al.* and Ferriera *et al.* (which were originally both part of a three-armed trial) all arms received immediate-release morphine as needed [319, 320]. For both studies, the immediate-release morphine was used significantly more frequently in the placebo group (8.7 vs. 5.8 and 7.0 vs. 4.2 daily doses, respectively) making an overall effect of the maintenance morphine more difficult to detect [319, 320]. Furthermore, in the study by Verberkt *et al.* there was a statistically significant effect on worst daily dyspnea measured on a numeric rating scale (NRS) in a subgroup of COPD patients with a modified Medical Research Council (mMRC) ≥ 3 (mean difference compared to placebo: − 1.33 (− 2.50 to − 0.16) points) [321]. Information on quality of life or health status was limited to four RCT's.

Of these, only the study by Verberkt *et al.* demonstrated a small positive, statistically significant effect on health status measured with the COPD assessment test (CAT) [321]. Our search identified no placebo-controlled RCT's investigating transdermal fentanyl for refractory dyspnea in COPD. Based on this assessment of available evidence, we designed a randomized, placebo-controlled clinical trial, on which we will further elaborate in the "Methods/ design" section and "Discussion" section.

**Table 1** | Overview of randomized clinical trials investigating the effect of opioids on dyspnea in COPD.

| Study | Design | n (% COPD) | Setting | Comparison | Treatment duration |
|---|---|---|---|---|---|
| **Woodcock 1981** [322] | Cross-over | 12 (100) | Outpatient | Dihydrocodeine | Single dose |
| **Light 1989** [323] | Cross-over | 13 (100) | Outpatient | Oral morphine 0.8 mg/kg | Single dose |
| **Jankelson 1997** [324] | Cross-over | 16 (100) | Outpatient | Nebulized morphine 20/40 mg | Single dose |
| **Noseda 1997** [325] | Cross-over | 14 (79)# | Hospitalized | Nebulized morphine 10/20 mg ±oxygen | Single dose |
| **Jensen 2012** [326] | Cross-over | 12 (100) | Outpatient | Nebulized fentanyl 50 µg | Single dose |
| **Abdallah 2017** [318] | Cross-over | 20 (100) | Outpatient | Morphine dose up to 10 mg | Single dose |
| **Iupati 2020** [327] | Cross-over Multicenter | 21 (62) | Outpatient | Intranasal fentanyl 20 µg as needed | 1 day |
| **Abernethy 2003** [313] | Cross-over Multicenter | 48 (88)# | Outpatient | SR morphine 20 mg od | 4 days |
| **Janowiak 2017** [328] | Cross-over | 10 (100) | Hospitalized | Nebulized morphine 3-5 mg qid | 4 days |
| **Johnson 1983** [314] | Cross-over | 18 (100) | Outpatient | Dihydrocodeine 15 mg prn tds | 7 days |
| **Currow 2020** [319] | Parallel Multicenter | 284 (58)# | Outpatient | SR Morphine 20 mg qd<br>All arms: morphine 2.5 mg prn | 7 days |
| **Ferriera 2020** [320] | Parallel Multicenter | 155 (60)# | Outpatient | Oxycodone 5 mg tds<br>All arms: morphine 2.5 mg prn | 7 days |
| **Eiser 1991** [329] | Cross-over | 14 (100) | Outpatient | Diamorphine 2.5/5 mg qid | 14 days |
| **Verberkt 2020** [321] | Parallel Multicenter | 124 (100) | Outpatient | SR Morphine 10 mg 1-tds | 28 days |
| **Poole 1998** [315] | Cross-over | 16 (100) | Outpatient | SR morphine 10 mg od or bid | 42 days |

**Table 1** | *Continued*

| **Breathlessness** | | |
|---|---|---|
| **Measurement (Scale)** | **Opioid** | **Placebo** |
| VAS (0-10 cm) 45 min after med | 5.54±1.91 | 6.33±2.0 |
| Borg (0-10) Rest | 0.29±0.58 | 0.13±0.23 |
| Borg score (0-10) After 6MWT | 4.2±2.1/ 4.3±1.8 | 4.3±2.2 |
| VAS (-100 to +100%) | +33±28/ +43±27 | +42±27 |
| Borg (0-10) Isotime CPET | 2.0±0.5 | 2.6±0.5 |
| Borg (0-10) Isotime CPET | 3.0±1.6* | 4.2±2.6 |
| VAS (0-100mm) 15 min after med | 26±21 (Δ29±25) | 21±19 (Δ33±24) |
| VAS (0-100mm) Morning/evening | 40.1±24*/ 40.3±23* | 47.7±26 49.9±24 |
| VAS (0-100mm) Now (2dd) | Δ25.4±9.0$ | Δ6.3±7.8 |
| VAS (0-10 cm) Mean daily | 4.6±2.1* | 5.6±2.3 |
| VAS (0-100mm) Now (2dd) | Δ-5.00±2.13 | Δ-4.86±2.07 |
| VAS (0-100mm) Now | Δ-3.7±2.9 | Δ-9.0±2.7 |
| VAS (0-10 cm) | 7.0±0.7/ 7.0±0.8 | 6.5±0.7 |
| NRS (0-10 points) Mean | Δ-0.60 (-1.55 to 0.35) | |
| DBS (0-5) | 2.22 | 2.26 |

*Table 1: Overview of randomized clinical trials investigating the effect of opioids on dyspnea in COPD. *p<0.05 opioid vs placebo, $ p<0.05 change after treatment. #data not exclusively on COPD. od = once a day, bid = twice daily, tds = three times a day, qid = four times a day, prn = as needed. SR = sustained release, VAS = Visual Analogue Score, DBS = Daytime breathlessness score, NRS = Numeric Rating Scale, CPET = cardiopulmonary exercise testing, 6MWT = 6-minute walking test, outp = outpatient, hosp = hospitalized. Data presented as mean±SD.*

**Table 2** | Overview of randomized clinical trials investigating the effect of opioids on quality of life or health status in COPD.

| Study | Design | n (% COPD) | Setting | Comparison | Treatment duration | Quality of life or health status | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Measurement (Scale) | Opioid | Placebo |
| **Currow 2020** [319] | Parallel Multicenter | 284 (58)# | Outpatient | SR Morphine 20 mg qd<br>All arms: morphine 2.5 mg prn | 7 days | EORTC-QLQ-C15 PAL (0-100) | Δ1.8±2.2 | Δ1.5±2.2 |
| **Ferriera 2020** [320] | Parallel Multicenter | 155 (60)# | Outpatient | Oxycodone 5 mg tds<br>All arms: morphine 2.5 mg prn | 7 days | EORTC-QLQ-C15 PAL (0-100) | Δ-1.7±3.1 | Δ2.82±3.1 |
| **Verberkt 2020** [321] | Parallel Multicenter | 124 (100) | Outpatient | SR Morphine 10 mg 1-tds | 28 days | CAT (0-40) | Δ-2.18 (-4.14 to -0.2)* | |
| **Poole 1998** [315] | Cross-over | 16 (100) | Outpatient | SR morphine 10 mg od or bid | 42 days | CRQ (20-140) | Δ2.08±4.53 | Δ2.94±3.46 |

**p<0.05 opioid vs placebo. #data not exclusively on COPD. od = once a day, bid = twice daily, tds = three times a day, qid = four times a day. SR = sustained release, CRQ = Chronic Respiratory Questionnaire, EARTC-QLQ-C15 PAL = Quality of life questionnaire developed by the European Organization for Research and Treatment of Cancer,, CAT = COPD assessment test. Data presented as mean±SD.*

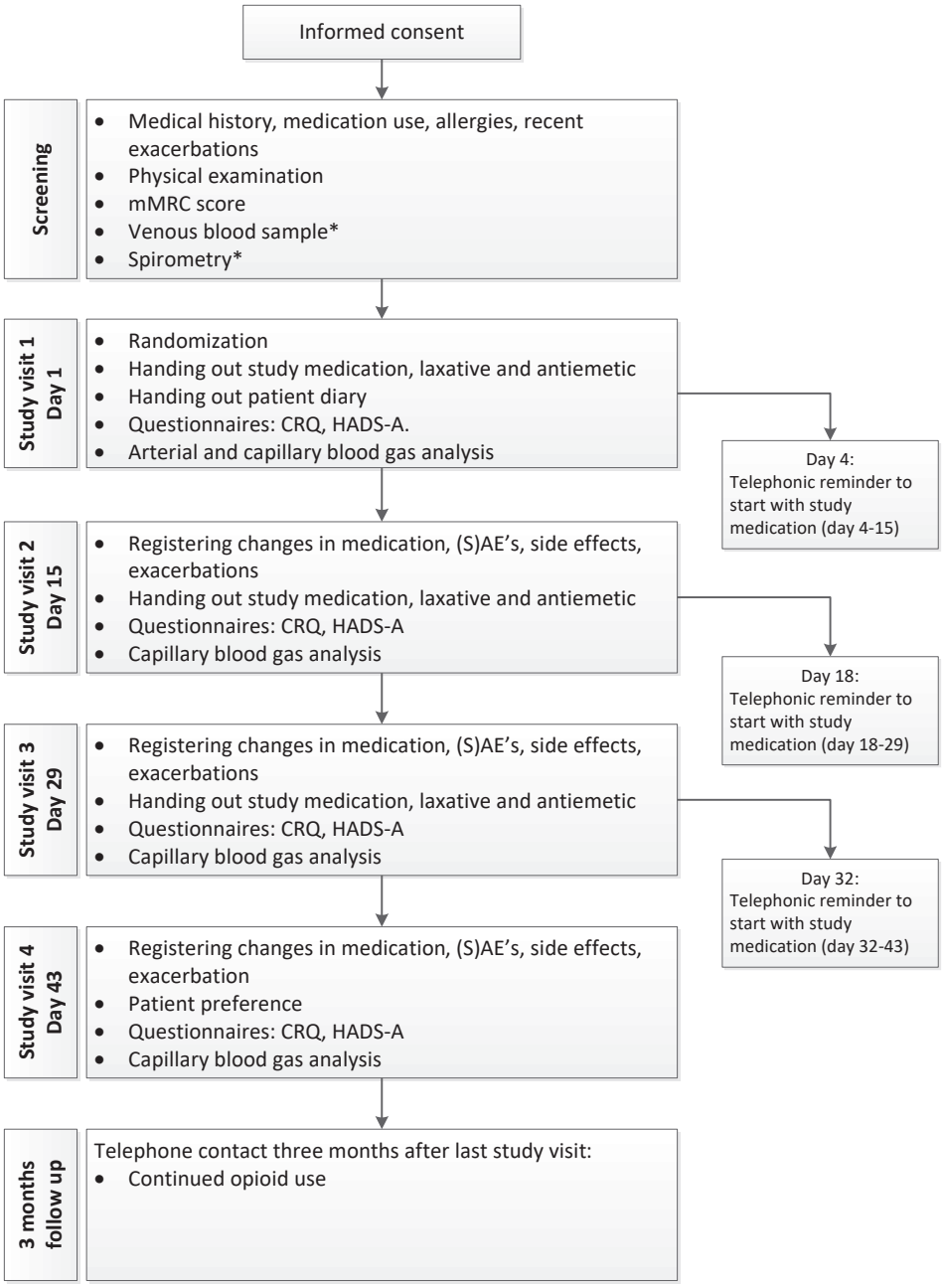


*Figure 1: Study flowchart. mMRC: modified Medical Research Council Score; CRQ: chronic respiratory questionnaire; HADS-A: hospital anxiety depression score—anxiety; (S)AE (serious) adverse event. *Unless already performed in the 6 months before screening.*

## Methods/design

*Overview*

We designed a robust, multi-center, double blind, double-dummy, cross-over, randomized, placebo-controlled clinical trial with three study arms investigating transdermal fentanyl and sustained-release morphine. We hypothesize that both fentanyl and morphine provide a reduction of dyspnea which is greater than placebo, and that fentanyl has less side effects than morphine. A total of 60 patients with severe stable COPD and refractory dyspnea will be included in this study in ten Dutch hospitals. Patients will be recruited at the outpatient clinic of each participating hospital by chest physicians. The study is registered at clinicaltrials.gov (NCT03834363), where a full list of participating hospitals can be found, and the protocol is approved by the UMCG Ethics committee. Written informed consent will be obtained from all participants and the study will be performed in accordance with the Declaration of Helsinki.

*Study duration and treatment*

The study duration is 6 weeks for each participant, divided in three periods of 2 weeks. During each period the participant is treated for 11 days. During the first 3 days of every treatment period no study medication is used, to wash out medication of any previous treatment period. The fentanyl patches are dosed 12 µg/h and changed every 3 days. The morphine sustained-released capsules are dosed 10 mg b.i.d. Both an antiemetic (metoclopramide 10 mg as needed, up to thrice daily) and laxative (macrogol/electrolytes 13.7 g, started once daily, more or less sachets as needed) are prescribed. In total, there are four study visits. A complete study flowchart can be found in Figure 1. After the end of the study treatment patients can discuss with their chest physician whether they would like to continue with low dosed morphine or transdermal fentanyl. At the time of this decision, the participants and physician are still blinded to the study treatment.

*In- and exclusion criteria*

All in- and exclusion criteria can be found in Table 3. In general, patients with COPD Gold class III or IV and a modified Medical Research Council score (mMRC) ≥ 3 who perceive dyspnea despite optimal standard therapy according to GOLD and the Dutch guideline for diagnosis and treatment of COPD can be included. If there is comorbidity substantially contributing to the breathlessness, for example severe heart failure, patients are excluded. Participants who have a moderate or severe exacerbation (requiring oral corticosteroids, antibiotics and/or hospital admission) during participation are discontinued from the trial. If they are stable for 8 weeks after recovery from the exacerbation, they are allowed to restart the study once more.

**Table 3** | In- and exclusion criteria.

| **Inclusion Criteria** |
|---|
| • Age ≥40 years. |
| • Read, understood and signed the Informed Consent form. |
| • COPD GOLD class III or IV, according to GOLD criteria. |
| • Post-bronchodilatation $FEV_1$/FVC < 70% and $FEV_1$ < 50% pred.* |
| • Complaints of refractory dyspnea as established by patient and doctor. |
| • mMRC score ≥ 3. |
| • Life expectancy of ≥ 2 months. |
| • Optimized standard therapy according to Dutch LAN guideline for diagnosis and treatment of COPD. |
| **Exclusion criteria** |
| • Other severe disease with chronic pain or chronic dyspnea (a non-susbstantial component of left sided heart failure is acceptable). |
| • Current use of opioids for whatever indication. |
| • Allergy / intolerance for opioids. |
| • Psychiatric disease, not related to severe COPD. |
| • Exacerbation of COPD 8 weeks prior to inclusion or between screening and randomization. |
| • Problematic (leading to medical help or social problems) substance abuse during the last five years. |
| • Active malignancy, with the exception of planocellular or basal cell carcinoma of the skin. |
| • eGFR <15 ml/min* |

** Measured within 6 months of screening. $FEV_1$: Forced Expiratory Value in 1 second; FVC: Forced Vital Capacity; LAN: Lung Alliance The Netherlands; mMRC: modified Medical Research Council Dyspnea Scale; eGFR: estimated Glomerular Filtration Rate.*

### *Outcome measurements*

The primary outcome measurement is change in mean daily dyspnea sensation as measured on the numeric rating scale for Dyspnea [330]. Secondary outcome measurements are change in worst daily dyspnea sensation, health-related quality of life, anxiety, sleep quality, occurrence of respiratory depression and side effects, patient preference and continued opioid use. A more extensive description of the outcome measures can be found in Table 4. Patients who drop out will be followed as much as possible for vital status, hospitalization, and start of open label opioids during the intended 6 weeks period of the study.

**Table 4** | Outcome measurements

| | Measurement | Frequency of measurement |
|---|---|---|
| **Primary outcome measure** | | |
| Change in mean dyspnea sensation | Numeric Rating Scale [330] | Once daily in patient diary |
| **Secondary outcome measures** | | |
| Change in worst dyspnea sensation | Numeric Rating Scale [330] | Once daily in patient diary |
| Change in Health-Related Quality of Life | CCQ [331] | Once daily in patient diary |
| | CRQ, CRQ-mastery domain [332] | During each study visit |
| Anxiety | HADS-A [333] | During each study visit |
| Side Effects | Open en named side effects | Once daily in patient diary and asked during each study visit |
| Change in hypercapnia, $HCO_3$ and pH | Capillary blood gas analysis | During each study visit |
| Change in Sleep Quality | Numeric Rating Scale [334] | Once daily in patient diary |
| Patient Preference | | Once |
| Continued opioid use | | Once |

*CCQ = Clinical COPD Questionnaire; CRQ = Chronic Respiratory Questionnaire; HADS-A = Hospital Anxiety and Depression Scale – anxiety subscale.*

## Randomization and unblinding

Randomization is tailor made for this study using a web based program (ALEA® DM version 17.1). Randomization can be performed online by the research team of each participating hospital. Participants will be randomized equally between the six possible treatment sequences, stratified for study location. Unblinding only occurs in the case of patient emergencies and at the conclusion of the study. Health authorities will be granted access to unblinded data if needed. The pharmacist on call of each participating hospital can unblind a participant using the web based program if requested by the researcher because of a patient emergency.

### *Statistical analysis*

For the power calculation the difference in primary endpoint between fentanyl and placebo was used. The Minimal Clinical Important Difference (MCID) for the NRS score is 1 point, the standard deviation is 2.0 points [335]. With a two-sided alpha = 0.05 and a power of 0.90 in a cross-over design, 44 participants who complete the study are needed. Because this is a fragile patient group, we will aim to recruit 60 participants.

The primary endpoint analysis will be on an intention to treat basis and therefore all patients randomized. The primary endpoint is the NRS mean dyspnea score which we will treat as a continuous variable for day 7–14. This will not be calculated if less than 2 days are available. Since it is a three way cross-over, the data for the available periods will also be used of not all periods were completed. No imputation will be used for the primary endpoint. There will be two comparisons: the difference in the mean dyspnea score of day 7–14 for fentanyl versus placebo and for morphine versus placebo. In this way, the risk of any remaining effect from the previous treatment periods influencing the outcome will

be optimally reduced. The analysis will be by Student's t-test. The analyses of secondary endpoints will be done by Student's t-tests (or non-parametric tests where needed) or chi square, following the same scheme of main comparisons as for the primary endpoints. The analysis of side effects will be done by comparison of proportions of side effects by chi square tests between all three arms. Composite questionnaire data will be primarily analyzed by total sum scores. Additionally, per protocol analyses will be performed. The study is not powered to determine equivalence of dyspnea relief of fentanyl compared to morphine: that comparison will consist of descriptive statistics only.

*Safety*

All (serious) adverse events will be monitored. The sponsor will report serious adverse events (SAEs) through the Dutch web portal ToetsingOnline to the accredited Ethics committee that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events. This is a short term study with 60 patients, entered parallel in a multi-center study. Therefore, and since opioids in the form of morphine are in the guidelines, we will not perform interim analyses, even though the patient population of patients with severe COPD and in a palliative setting is at increased risk of death. For the same reasons, no Data Safety Monitoring Board (DSMB) will be instituted.

*Study timeline*

The study has started in November 2019. At this point the first participant was included at the University Medical Center Groningen. For the other participating hospitals the start of inclusion was delayed by one or more months because of a delay in the production of research medication and a delay in the issuing of a permit for scientific research with opioids for the participating hospital pharmacies. Unfortunately, starting March 2020 the inclusion was alternately put on hold or restricted in each participating hospital due to the COVID-19 pandemic. We aim to include all patients by the end of 2021, but whether this will be achieved is strongly depended on the course of the COVID-19 pandemic.



## Discussion

Optimal reduction of dyspnea in patients with severe COPD is an important way to improve quality of life, yet can be very challenging. From our assessment of the literature, we found that even though opioids have found their way into COPD guidelines as a treatment option for refractory dyspnea, the evidence base can still be considered inconclusive. Furthermore, the majority of research has focused on morphine and we identified no placebo- controlled RCT investigating transdermal fentanyl. However, trials investigating fentanyl in the short-acting form, suggest that fentanyl could give a reduction of dyspnea [336, 337]. Additionally, studies on pain treatment indicate that patients may prefer transdermal fentanyl and

experience less side effects in comparison to oral morphine [338]. Therefore, we believe that our current multi-center, double blind, cross-over, placebo-controlled study design to investigate sustained-release morphine and transdermal fentanyl for refractory dyspnea will provide valuable information on patient preference and the effectiveness. By choosing a cross-over design for this study the participant is his or her own control, thus reducing the variability and the number of patients needed to participate. Additionally, this design helps to get a better impression of patient preferences. On the other hand, because of the cross-over design the treatment duration is 6 weeks instead of 11 days (which it would be if this study had a parallel design). This prolonged study duration will most likely increase the risk of participants that have to be discontinued from the trial because of the occurrence of COPD exacerbations, which occur frequently in advanced COPD. For this reason we aim to include 60 participants, which is sixteen more than the 44 participants calculated from the power analysis which need to fully complete the study. Furthermore, patients experiencing an exacerbation will discontinue the trial, but may be included once more if they are clinically stable for at least 8 weeks.

There are indications that prescription of opioids for refractory dyspnea in COPD can be a loaded topic for both patient and doctors, amongst others because of associations with terminal disease, possible adverse effects and addiction [150]. Although this has not been formally investigated in patients, we believe education is important to address any questions or worries patients may have regarding opioids. Therefore, both an animated short film for patients and their loved ones on facts and myths about opioids (developed by Indiveo B.V.) as well as an information leaflet with the same content are tested during our study. At the end of the trial, feedback from the participants will be used to adjust the animation and leaflet and these will be made widely available for patients with COPD. Additionally, both patients and physicians participating in the study are asked to share their experiences with opioids for refractory dyspnea in COPD during regional congresses and meetings.



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**Author's contributions:** HAK, SMH and KMM initiated the trial. MD and HAK wrote the research protocol and acquired funding for the trial. All authors were involved in the development of the study design and study protocol, and have approved the submitted version of the protocol. All authors include patients and collect and check data. MD is the coordinating researcher, and HAK is principal investigator.

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**Protocol version:** Protocol version 14, date 14th February 2020, has been approved by the ethics committee of the University Medical Center Groningen Medical Research.

**Availability of data and materials:** The data management plan is made available in de the online supplement (Additional file 1 - Online supplement MoreFoRCOPD). Marlies (M.) van Dijk or Huib (H.A.M.) Kerstjens can be contacted to apply for permission to obtain access to the raw data that will be generated during the study.

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**Ethics approval and consent to participate:** The study is designed in accordance with the Declaration of Helsinki and approved by the ethics committee of the University Medical Center Groningen Medical Research Ethics committee (Netherlands). All amendments will be communicated with relevant parties. Written informed consent will be obtained from all participants by a member of the research team of each participating hospital. Each participant will be covered by insurance in case of unexpected harm from participating in the trial.

**Consent for publication:** The ethical approval and patient information include consent to publish collected data.

**Competing interests:** MD, KMM, JWB, WB, RH, SMH, WYL, LEP, KP, HAK report no competing interests related to this study.

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## Supplementary material

### *Search strategy*

Study design: Placebo-controlled randomized clinical trials.

Study treatment: Any type of opioid prescribed for dyspnea reduction.

Study population: COPD patients (≥ 50% of total number of participants)

Study endpoints: Dyspnea, quality of life and/or health status.

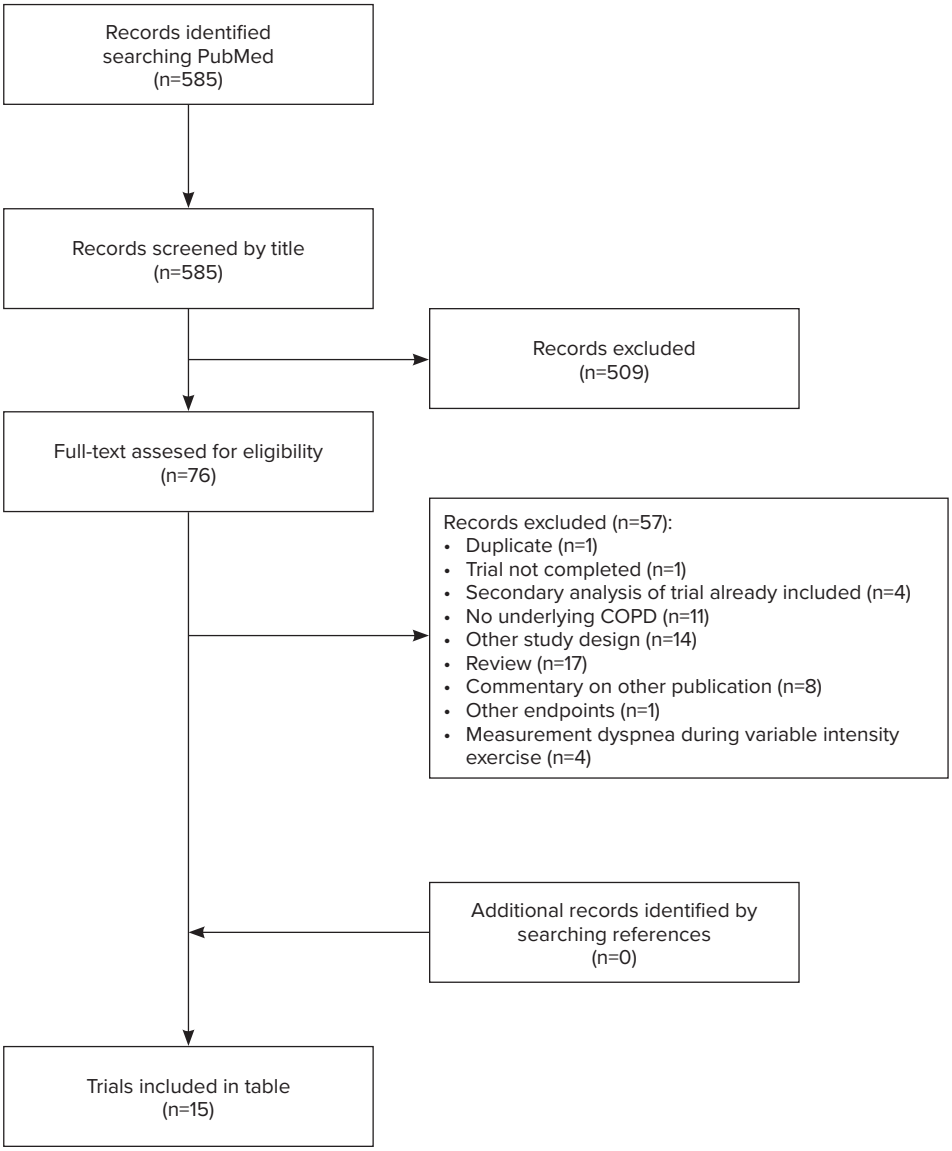


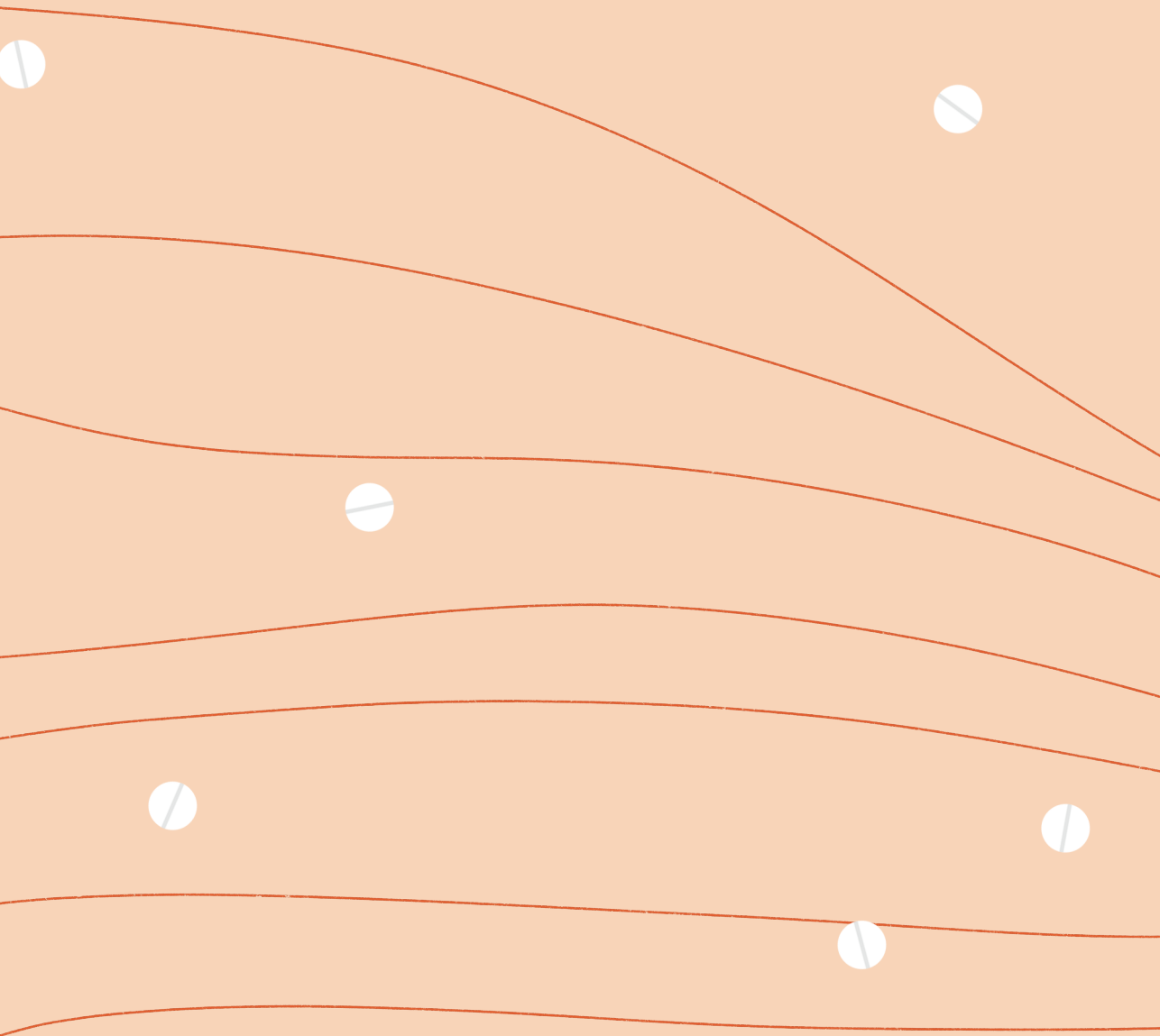
PubMed search:

Performed on: 26th March, 2021.

("morphine"[Title/Abstract] OR "codeine"[Title/Abstract] OR "fentanyl"[Title/Abstract] OR "dihydrocodeine"[Title/Abstract] OR "diamorphine"[Title/Abstract] OR "Oxycodone"[Title/Abstract] OR "Hydrocodone"[Title/Abstract] OR "Methadone"[Title/Abstract] OR "buprenorphine"[Title/Abstract] OR "meperidine"[Title/Abstract] OR "hydromorphone"[Title/Abstract] OR "oxymorphone"[Title/Abstract] OR "tramadol"[Title/Abstract] OR "carfentanil"[Title/Abstract]) AND ("COPD"[Title/Abstract] OR "Chronic obstructive"[Title/Abstract] OR "airflow obstruction"[Title/Abstract] OR "dyspn*"[Title/Abstract] OR "breathlessness"[Title/Abstract])

## Study flowchart





CHAPTER 10

# Summary

The goals of this thesis were twofold: first, to increase physiological insight in lung volume reduction treatments, in order to improve and potentially expand patient selection and optimally balance the chance of successful treatment with the chance of unwanted adverse reactions. Additionally, this thesis aimed to improve the treatment of refractory dyspnea in COPD by investigating low dose opioids.

The studies that are part of this thesis are summarized below.

Treatment options for severe stable COPD on top of standard of care are described in **chapter 2**. These treatment options are discussed on the basis of treatable traits and are illustrated by a case study. Amongst others, bronchoscopic lung volume reduction (BLVR) (for hyperinflation), non-invasive ventilation (for hypercapnic respiratory insufficiency), pulmonary rehabilitation (when multiple extrapulmonary and pulmonary treatable traits are simultaneously present), and lung transplantation (in case all treatable traits are optimally addressed and a severe disability remains), are discussed. Furthermore, a case is made for a multidimensional approach to optimize personalized treatment for each patient with severe COPD.

Lung volume reduction (LVR) treatment in patients with severe emphysema has been shown to have a positive effect on hyperinflation, expiratory flow limitation, exercise capacity and quality of life. However, the effects on the diffusing capacity of the lungs and gas exchange are less clear. In **chapter 3**, the possible mechanisms by which LVR treatments can affect diffusing capacity and gas exchange are discussed. The use of the diffusing capacity of the lungs for carbon monoxide ($DL_{CO}$) in LVR treatment is evaluated and other diagnostic techniques reflecting diffusing capacity and regional ventilation ($V'$)/perfusion ($Q'$) mismatch are considered. Additionally, a systematic review of the literature was performed for studies reporting on $DL_{CO}$ and arterial blood gas parameters before and after LVR surgery or endoscopic LVR with endobronchial one-way valves. $DL_{CO}$ after these LVR treatments significantly improved (40 studies, n=1855) and the mean absolute change from baseline in % predicted $DL_{CO}$ was +5.7% (range −4.6% to +29%), with no real change in blood gas parameters. Improvement in ventilation inhomogeneity and ventilation perfusion mismatch are plausible explanations for the observed improvement in $DL_{CO}$ after LVR.



In **chapter 4** a single-center retrospective analysis is described investigating the safety and effectiveness of endobronchial valve treatment in patients with emphysema and a $DL_{CO}$ ≤20%pred, a group commonly excluded from clinical trials investigating endobronchial valves. Outcome parameters were compared to a historical matched control group with $DL_{CO}$ >20%pred. Twenty patients (80% female, 64 ± 6 years, $FEV_1$ 26 ± 6%pred, RV 233 ± 45%pred, $DL_{CO}$ 18 ± 1.6%pred) underwent EBV treatment. At 6 months follow-up, we found a statistically significant improvement in $FEV_1$ (0.08 ± 0.12 L), RV (–0.45 ±0.95 L), 6 min walk distance (38 ± 65 m), and St. George's Respiratory Questionnaire (–12 ± 13 points). With the exception of $FEV_1$, all exceeded the minimal clinically important difference. The most common serious

adverse event was a pneumothorax requiring intervention (15%). There were no significant differences in outcome compared to the matched control group with $DL_{CO}$ >20%pred. From this single-center retrospective analysis we concluded that statistically significant and clinically relevant improvements in lung function, exercise capacity, and quality of life up to 6 months after EBV treatment are feasible in selected emphysema patients with a $DL_{CO}$ ≤20%pred (14–20%) with no increased risk of serious adverse events.

In patients with severe emphysema, dynamic hyperinflation is superimposed on top of already existing static hyperinflation. Static hyperinflation reduces significantly after bronchoscopic lung volume reduction, and it is widely accepted that dynamic hyperinflation does as well. In **chapter 5**, we described a single center prospective cohort study to investigate the effects of bronchoscopic lung volume reduction compared to standard of care (SoC) on dynamic hyperinflation. Dynamic hyperinflation was induced by a manually paced tachypnea test (MPT) and was defined by change in inspiratory capacity (IC) measured before and after MPT. Static and dynamic hyperinflation measurements were performed both at baseline and 6 months after bronchoscopic lung volume reduction with endobronchial valves or coils (treatment group) or SoC (control group). Eighteen patients underwent BLVR (78% female, 57 (43–67) years, $FEV_1$ 25 (18–37) %predicted, residual volume 231 (182–376) %predicted). Thirteen patients received standard of care (100% female, 59 (44–74) years, $FEV_1$ 25 (19–37) %predicted, residual volume 225 (152–279) %predicted. The 6 months median change in dynamic hyperinflation in the treatment group was: + 225 ml (range − 113 to + 803, $p<0.01$) vs 0 ml (− 1067 to + 500, $p=0.42$) in the control group, the difference between the groups being significant ($p<0.01$). An increase in dynamic hyperinflation was significantly associated with a decrease in residual volume ($r=-0.439$, $p<0.01$). We concluded that bronchoscopic lung volume reduction increases the ability for dynamic hyperinflation in patients with severe emphysema. We propose this is a consequence of the improved static hyperinflation.

For **chapter 6**, we performed another single center prospective study aimed to compare dynamic hyperinflation measured by cardiopulmonary exercise testing (CPET), a 6-min walk test (6-MWT), and a manually paced tachypnea test (MPT) in patients with severe emphysema who were treated with endobronchial coils. Additionally, we investigated whether dynamic hyperinflation changed after treatment with endobronchial coils. Twenty nine patients underwent dynamic hyperinflation testing before and after coil treatment. There was no significant change in dynamic hyperinflation after treatment with coils. Comparison of CPET and MPT induced dynamic hyperinflation (including all measurements, baseline and follow up) showed a strong association (rho 0.660, $p<0.001$) and a moderate agreement (BA-plot, 202 ml difference in favor of MPT). There was only a moderate association of the 6-MWT with CPET induced dynamic hyperinflation (rho 0.361, $p$ 0.024). The results of this study led us to conclude that MPT can be a suitable alternative to CPET to measure dynamic hyperinflation in severe emphysema, but may overestimate dynamic hyperinflation possibly due to a higher breathing frequency.

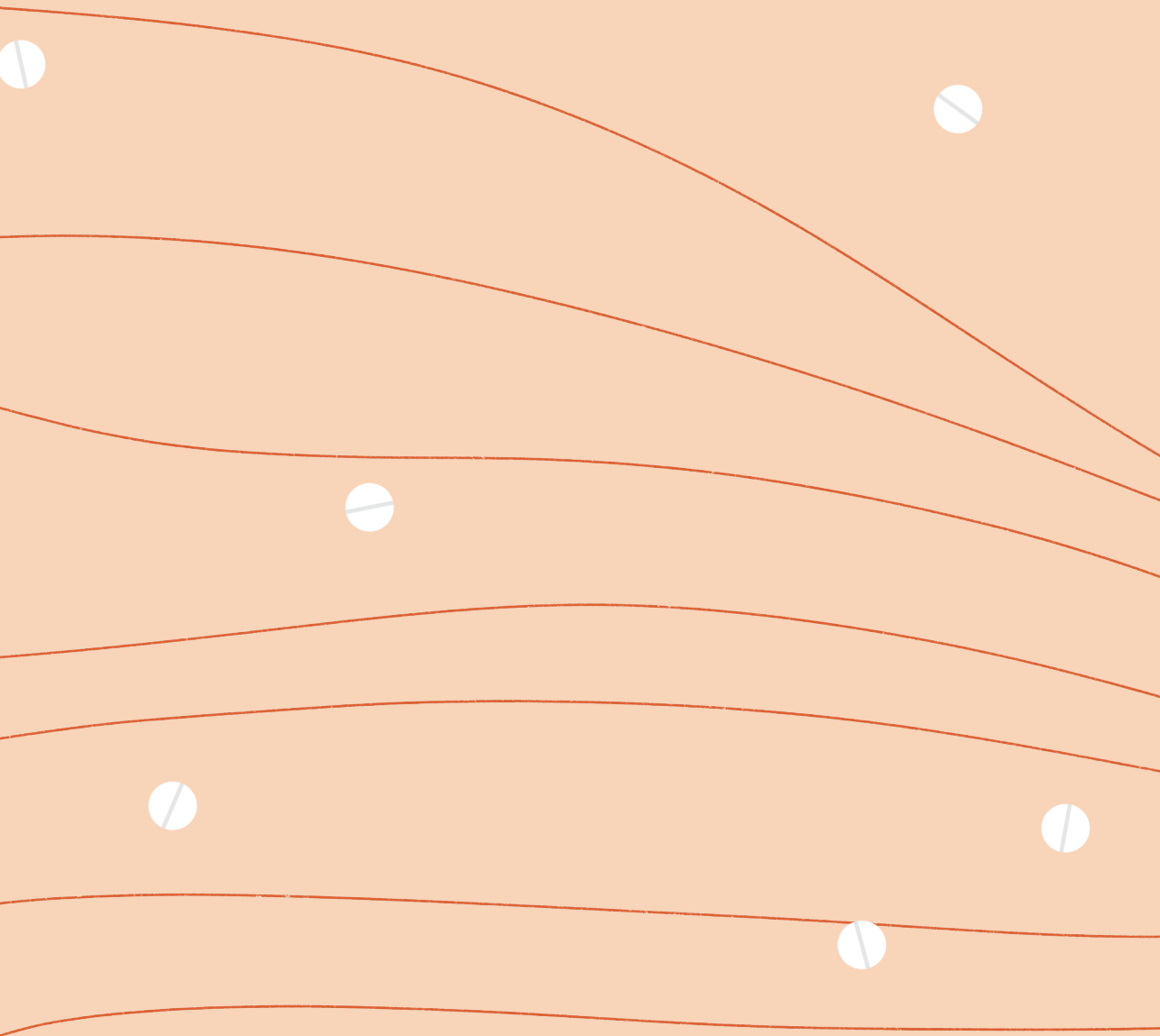
In **chapter 7** we describe a single-center prospective open label study, to evaluate the feasibility, safety, and efficacy of a new size endobronchial valve (size "5.5-Low Profile" (LP) EBV), which has been developed to accommodate airways that are wide but have a short "landing zone". Patients were included if eligible for valve treatment with a local anatomy suitable to place at least one 5.5-LP EBV. Feasibility, safety, CT parameters, pulmonary function tests, and questionnaires were assessed at baseline and 6 weeks after treatment. In total, we included 30 patients ($FEV_1$ 29 ± 10%; RV 242 ± 46%; and quality of life measured by the SGRQ 56 ± 11 points). In addition to the other valve sizes, a median of 1 (1–3) 5.5-LP EBV was placed; no immediate valve adjustment was needed. One patient developed an asymptomatic pneumothorax, and 4 revision bronchoscopies were performed due to absence of clinical benefit, which was related to the dislocation of a 5.5-LP EBV in one patient. Clinically relevant improvements were seen in target lobar volume reduction –1,554 mL, $FEV_1$ +39%, RV –960 mL, and SGRQ –18 points. In this first in human study, the 5.5-LP EBV could be placed without unexpected complications and with good efficacy outcomes.

The most common complication of BLVR with one-way valves is a pneumothorax with a reported prevalence of up to 34% of treated patients. Provided patient selection is optimized, the risk-to-benefit ratio of a pneumothorax appears to be acceptable as many of these patients still develop substantial improvements in functional outcomes after resolution of the pneumothorax. However, the occurrence of a pneumothorax and its management should be considered routine clinical care to the entire team when performing BLVR with valves in patients who have progressive disease, severely compromised lung tissue, and limited therapeutic options. Timely resolution of a post-valve treatment pneumothorax requires skilled and adequate pneumothorax management. **Chapter 8** consists of an expert panel statement, which is an updated recommendation of the 2014 post-valve treatment pneumothorax statement. The recommendations in this chapter are based on a combination of the current scientific literature and expert opinion, which was obtained through a modified Delphi method. A pragmatic management plan for post-valve treatment pneumothorax is proposed attempting to guide physicians in daily practice. Additionally, mechanisms for pneumothorax development, risk assessment, prevention of pneumothorax, and outcomes after pneumothorax are addressed.

10

Refractory dyspnea or breathlessness is the most common symptom in patients with advanced chronic obstructive pulmonary disease (COPD), with a high negative impact on quality of life (QoL). Low dosed opioids have been investigated for refractory dyspnea in COPD and other life-limiting conditions, and some positive effects were demonstrated. However, upon first assessment of the literature, the quality of evidence in COPD seemed low or inconclusive, and focused mainly on morphine which may have more side effects than other opioids such as fentanyl. For **chapter 9** we performed a systematic literature search. We searched for placebo-controlled randomized clinical trials investigating opioids for refractory dyspnea caused by COPD. We included trials reporting on dyspnea, health status and/or QoL. Three of fifteen trials demonstrated a significant positive effect of opioids

on dyspnea. Only one of four trials reporting on QoL or health status, demonstrated a significant positive effect. Two-thirds of included trials investigated morphine. We found no placebo-controlled RCT on transdermal fentanyl. Subsequently, we hypothesized that both fentanyl and morphine provide a greater reduction of dyspnea than placebo, and that fentanyl has less side effects than morphine. We designed a robust, multi-center, double blind, double-dummy, cross-over, randomized, placebo-controlled clinical trial with three study arms investigating transdermal fentanyl 12 mcg/h and morphine sustained-release 10 mg b.i.d. The crossover design will help to get a better impression of patient preferences. The primary endpoint is change in daily mean dyspnea sensation measured on a numeric rating scale. Secondary endpoints are change in daily worst dyspnea, quality of life, anxiety, sleep quality, hypercapnia, side effects, patient preference, and continued opioid use. Sixty patients with severe stable COPD and refractory dyspnea ($FEV_1$ < 50%, mMRC ≥ 3, on optimal standard therapy) will be included to achieve full evaluable data on 44 patients. We believe our study design to investigate both sustained-release morphine and transdermal fentanyl for refractory dyspnea will provide valuable information for better treatment of refractory dyspnea in COPD.



CHAPTER 11

# General discussion and future perspectives

Historically, the treatment options for severe COPD have been limited. But fortunately, these days there are multiple options which can improve quality of life and sometimes even survival in patients with severe COPD. In Chapter 2 we describe treatment options for patients with severe, stable COPD by identification of treatable treats. The treatment options for severe COPD range from simple, low cost treatments such as macrolides or low dosed opioids to advanced, costly treatment options such as bronchoscopic lung volume reduction (BLVR), lung transplantation and non-invasive ventilation, which require dedicated centers with specialized physicians and nurses. The high costs and sometimes scarcity (*e.g.* lung transplantation, availability and reimbursement of novel medical devices) of these advanced treatment options highlight the importance of reserving these treatments for patients who are most likely to have a good response. In our opinion, this means that patients should be on optimal standard therapy for COPD before considering these advanced treatment options. On the other hand, this does not relieve physicians and specialized nurses of the responsibility to evaluate treatable traits in depth for each patient with COPD and to consider whether referral to a specialized center is indicated. There may still be room for improvement with regard to optimizing standard therapy. Real life data from 65 patients who visited our 'severe COPD - lung failure' outpatient consultation indicated that only 49% of patients were currently receiving physiotherapy, and 60% of patients had never taken part in a rehabilitation program. Additionally, in 59% of patients advice regarding pharmacological treatment (specifically on inhalation medication, oral corticosteroids, antibiotics) was given to the referring physician.

A challenge to optimize the personalized treatment for patients with COPD may be that amongst both physicians and patients the change in perspective for severe COPD is not always common knowledge, leading to an ongoing sense of hopelessness and inertia. Additionally, it may currently not be clear enough which patients with COPD should be evaluated for the more "advanced treatment options". The current international GOLD guidelines do provide a classification for COPD severity based on complaints, frequency of exacerbations and airflow obstruction. However, in contrast with the asthma guidelines, there is no clear distinction between difficult-to-treat and severe COPD, and controlled and uncontrolled COPD. We propose that a comparable framework for COPD could help optimize standard therapy and referral for advanced treatment options. As a starting point for discussion, we propose the following definitions:

**Uncontrolled COPD:** COPD with persisting complaints (CAT> 10, CCQ > 1.0) and/or frequent exacerbations (≥2 per year, or at least one hospital admission). (*i.e.* COPD Gold Class B, C, or D)

**Difficult-to-treat COPD:** Uncontrolled COPD despite treatment with bronchodilators and -when indicated- inhaled corticosteroids, where there is still room to optimize standard therapy.*

**Severe COPD:** Difficult-to-treat COPD despite optimal standard therapy.

Consider referral for evaluation of advanced treatment options in case of uncontrolled, severe COPD.

**Optimal standard therapy for COPD includes: Education on COPD and self-management, guided smoking cessation attempts, optimized inhalation medication (including regular instructions) and vaccinations (Pneumococcal, Influenza, SARS-Cov-2), a maintenance physical activity program, and as indicated: nutritious support, optimal treatment of comorbidities, macrolide maintenance therapy, long term oxygen therapy, sputum clearance techniques, and outpatient pulmonary rehabilitation.*

We propose that there is room for improvement in the organization of COPD care, including multidisciplinary team (MDT) meetings to discuss challenging cases, and the possibility to refer to expertise centers for evaluation of advanced treatment options such as clinical rehabilitation, non-invasive ventilation, lung volume reduction treatment, lung transplantation, and biologicals (within clinical trials). For other subspecialties within pulmonology, such as thoracic oncology and interstitial lung disease, this is already common practice in The Netherlands. In Chapter 2 we describe our multidimensional approach in evaluating patients with COPD, including an MDT. To provide a scientific basis, investigating the effect on both patient-related outcomes and health care utilization for this approach would be interesting. Including a control group in this analysis would strengthen the quality of the investigation, but could be challenging to carry out in clinical practice. A mixed background (several hospitals) historical control cohort would perhaps be feasible.

A large part of this thesis (chapter 3 to 8) concerns lung volume reduction treatment. The most commonly performed lung volume reduction treatment is bronchoscopic placement of endobronchial valves, for which multiple trials have demonstrated a significant and clinically relevant effect on lung function, exercise tolerance and quality of life in selected patients [32-35]. Unfortunately, the majority of patients with COPD and severe hyperinflation are ineligible for endobronchial valve treatment. One important factor for ineligibility is an incomplete interlobar fissure adjacent to the target lobe. This causes collateral ventilation between the target lobe and ipsilateral lobe(s), which subsequently prevents volume reduction of the target lobe, and renders the treatment ineffective. If there was a way to

repair a fissure defect, this could lead to an important increase in the number of COPD patients eligible for treatment with endobronchial valves. Therefore, we believe fissure repair is an important direction for further research relating to endobronchial valves. Currently, the possibility to repair a fissure defect is investigated in two trials, the CONVERT trial (NCT04559464), and the Mind The Gap-Crossing borders trial (NCT04256408). Both trials investigate the placement of Aeriseal (Pulmonx Corporation, Redwood City, CA), which is a two component foam, which has previously been investigated as lung volume reduction technique, at the location of the fissure defect. The Aeriseal® is administered endobronchially for the CONVERT trial, and transbronchially for the Mind The Gap-Crossing Borders trial, with the help of navigational software (Bronchus Archimedes™). If these trials demonstrate the proof of concept that fissure defects can be repaired, investigating more biocompatible adhesives for this indication could prove to be an interesting next step, since synthetic, less biocompatible adhesives such as Aeriseal® can induce severe inflammatory response and adverse events such as exacerbations and hemoptysis. Additionally, a biocompatible adhesive which is suitable for fissure repair, may also be eligible as lung volume reduction modality in itself, when administered to the most emphysematous parts of the lungs. However, as described by a recent review on crosslink bio-adhesives of Joglekar *et al*, this development does come with challenges of its own, since the bio-adhesive should be, amongst others, non-degradable, cause no important immune response, and be able to withstand a wet and dynamic environment (*i.e.* the lungs) [339].

Another challenge for bronchoscopic lung volume reduction with endobronchial valves, is loss of lung volume reduction effect in patients who initially experience a positive effect from the valve treatment. This loss of effect is most often caused by formation of granulation tissue around the valves, which can subsequently cause dislocation of valves and hemoptysis. One study reported granulation tissue in up to 53% of patients who underwent a revision bronchoscopy [340]. Although the formation of granulation tissue is a well-known phenomenon in response to the placement of endobronchial devices in general, knowledge on the pathophysiology of granulation tissue formation is still very limited [341]. Future research unraveling the underlying mechanism of granulation tissue formation, which probably involves both device-related and patient-related factors [341], is important as a starting point for prevention and/or treatment of granulation treatment in response to endobronchial valves and other devices placed in the airways.

Another bronchoscopic lung volume reduction technique which is part of the international GOLD guidelines for treating COPD, is treatment with endobronchial coils [342]. This is a non-blocking technique which has also been demonstrated to improve lung function, exercise tolerance and quality of life [38]. Eligibility for endobronchial coils is not dependent on intact interlobar fissures, which is an important advantage over endobronchial valves. Furthermore, since this is a non-blocking technique (*i.e.* no atelectasis is induced), hardly any gas exchange surface is sacrificed to achieve lung volume reduction, which may be especially of value in patients with impaired gas exchange and a homogeneous distribution

of emphysema. Up until now, the mean effect of bronchoscopic lung volume reduction with coils appears to be somewhat less pronounced than endobronchial valve treatment, and it is more difficult to predict beforehand whether the patient will be a responder or not to treatment. Additionally, due to a business decision, the nitinol coils which have been investigated in previous trials, are no longer produced. However, this does not alter the fact that there is still a group of patients with COPD and severe hyperinflation which could profit from this type of treatment, for example patients who have a large interlobar fissure defect adjacent to the target lobe(s). A new type of coil, which could be better described as a lung tensioning device (FreeFlowMedical, CA, USA), has been developed and is currently being investigated in a first in-human trial (NCT04520152). Hopefully, in the coming years, this and additional trials will provide important information on the safety, effectiveness and optimal patient selection for this type of lung volume reduction treatment.

Another possible, and potentially elegant mechanism to reduce hyperinflation and air trapping is by creating alternative ways for the air to be released from emphysematous parts of lungs (*i.e.* airway bypass), or increasing the diameter of existing small airways during expiration. This concept has been investigated in the past in the EASE trial, a sham-controlled RCT where up to 6 Exhale® drug-eluting stents (Broncus technologies, CA, USA) were placed in the airways of patients with severe hyperinflation and homogeneously distributed emphysema [343]. In the very short term, this resulted in important improvements of $FEV_1$, residual volume and quality of life. However, mainly due to occlusion of the stents, this effect unfortunately did not last. This study demonstrated both the potential of this kind of lung volume reduction technique, as well as the challenge to keep devices functional in the airways. New devices are on their way, for which future research will have to prove whether they can achieve long term effects, by withstanding amongst others mucus plugging and the formation of granulation tissue. One upcoming open-label trial will investigate the Pulmair Implantable Artificial Bronchus (IAB, Pulmair Medical, CA, USA) [NCT05087641]: this device will be placed in the bronchi with the goal to achieve better deflation of the target lobe.

Finally, another way to achieve bronchoscopic lung volume reduction is by inducing a localized inflammatory response in the most emphysematous parts of the lung. This has been investigated previously with heated water vapor and the above mentioned Airiseal® [69, 344]. However, even though there are indications that both treatment modalities may lead to improved lung function and quality of life, the potential severity of adverse events (most importantly pneumonitis, acute inflammatory response in the lung, and pneumonia) may have prevented these treatments from being performed and investigated more widely.

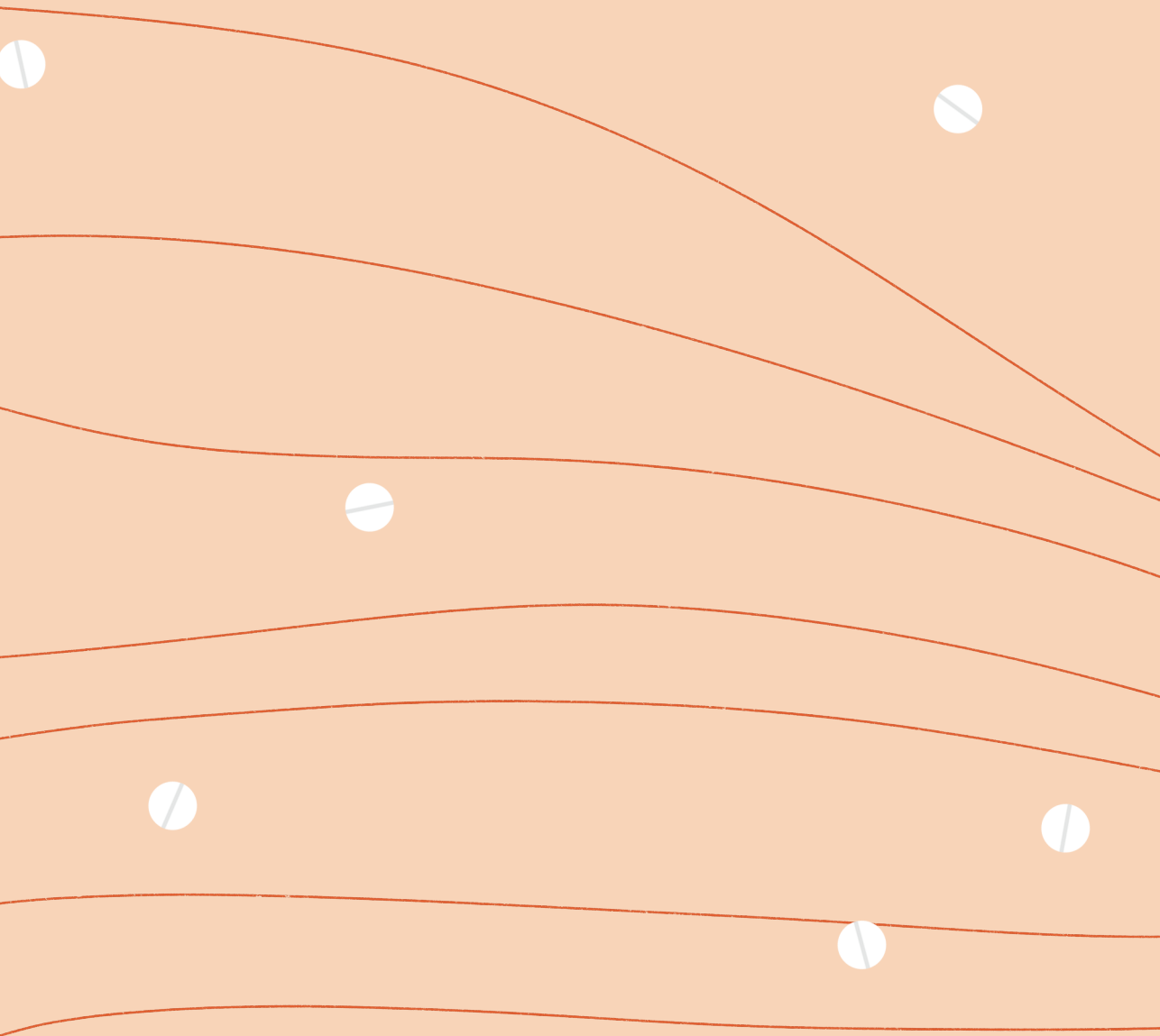


By investigating the effect of lung volume reduction treatment on diffusing capacity and gas exchange in chapter 3, and the outcomes of lung volume reduction treatment with a very low diffusing capacity in chapter 4, our interest grew in determinants of gas exchange in patients with severe COPD. Of course, many factors are known to influence gas exchange in COPD, such as emphysema, airflow obstruction, pulmonary hypertension and obesity.

However, we believe that gas exchange in COPD is still incompletely understood, since there is a great variation in the range of gas exchange impairment in the large number of patients with severe COPD we see in our bronchoscopic intervention center, even if we match patients for severity of emphysema, airflow obstruction, and the presence of pulmonary hypertension.

We propose that the vascular component of COPD may play an undervalued part in gas exchange, and that abnormalities could comprise more than pulmonary hypertension, which is a well-known phenomenon in patients with severe COPD. By using a wide range of techniques, ranging from pulmonary endothelial cell lines in the laboratory, and pathological evaluation of lung tissue to imaging techniques such as chest CT and MRI, and quantitative analysis of vessels on CT scan, and correlating these outcomes to extensive clinical phenotyping (*i.e.* baseline characteristics, pulmonary function testing, arterial blood gas analysis), we hope to get more insight into the pulmonary vascular component of COPD.

Chapter 9 describes our trial design investigating low dosed opioids for refractory dyspnea in COPD. An interesting phenomenon with regard to this subject is that this treatment option has already been adapted in national and international guidelines, while the level of evidence is considered to be low to very low. Of course, we hope that the outcomes of our trial will bring more clarity on the subject, either with a clear positive or negative outcome. However, even if the study demonstrates a positive effect of opioids on refractory dyspnea, we believe it will still be relevant to investigate other treatment options for refractory dyspnea in COPD, since it is unlikely that all COPD patients with refractory dyspnea respond to opioids. In fact, it would be interesting in the future to investigate which factors influence the likelihood to respond to opioids. Some preliminary work has been done in this field, suggesting age and underlying anxiety as possible factors influencing response to opioids for dyspnea [345]. Another hypothesis could be that the underlying mechanism for a dyspnea episode, such as dynamic hyperinflation, neuro-mechanical dissociation or hypoxemia, also influences the chance of a positive response to opioids. However, this may be challenging to investigate, as doing so would require taking measurements in real time as the patients suffers from a dyspnea episode in the outpatient setting. Next to opioids, we propose non-pharmacological options may hold the most promise for improved management of refractory dyspnea in the future. There have been some small studies investigating the effect of a portable, handheld non-invasive ventilation device (Philips, Respironics, Morrisville, PA, USA) which can be used as needed in case of a dyspnea episode [346, 347]. Although results were mixed overall, one trial including 24 COPD patients demonstrated a positive effect on exercise-induced dyspnea, exercise tolerance, dyspnea recovery time and quality of life. A larger, preferably sham-controlled randomized clinical trial, is needed to further investigate the effect and feasibility of this device. Additionally, it would be interesting to investigate the mechanism of action, and we hypothesize that this is a reduction of dynamic hyperinflation.



CHAPTER 12

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**APPENDICES**

# Nederlandse samenvatting

# Dankwoord

# Curriculum Vitae & publicatielijst

# Nederlandse samenvatting

## COPD

COPD staat voor ‘chronic obstructive pulmonary disease’, ofwel ‘chronische obstructieve longziekte’. Het is een ziekte die veel voorkomt, alleen al in Nederland bij ongeveer 600.000 personen. Ook is COPD wereldwijd de derde doodsoorzaak. Roken is de belangrijkste risicofactor om COPD te ontwikkelen, in Nederland heeft 90% van de patiënten met COPD gerookt. Andere risicofactoren zijn onder meer: blootstelling aan fijnstof, giftige gassen en dampen, rook van houtvuur, en een tekort aan het alfa-1-antitrypsine-eiwit.

De meest voorkomende klachten bij COPD zijn kortademigheid en slijm ophoesten. Met name bij ernstiger vormen van de ziekte komen ook meer algemene klachten zoals vermoeidheid en gewichtsverlies voor. Van dag tot dag kan de ernst van de klachten variëren. Daarnaast komen COPD-longaanvallen voor, waarbij de klachten van kortademigheid en slijm ophoesten gedurende dagen tot weken kunnen verslechteren. Ook is COPD geassocieerd met een verhoogd risico op andere ziektes, zoals hart- en vaatziekten, botontkalking en depressies. De combinatie van dagelijkse klachten, een verminderd inspanningsvermogen, longaanvallen en bijkomende ziektes, beïnvloedt de kwaliteit van leven bij COPD vaak negatief.

COPD is een aandoening van de luchtwegen (bronchitis) en het longweefsel (verlies van longblaasjes, emfyseem). Kenmerkend voor COPD is dat er een luchtwegvernauwing (bronchusobstructie) is, waardoor de luchtwegweerstand toeneemt en de uitademing bemoeilijkt is. Ook kan er, met name bij de aanwezigheid van emfyseem, zogenaamde ‘hyperinflatie’ ontstaan. Bij hyperinflatie neemt de longinhoud toe en blijft er ook na uitademing te veel lucht achter in de longen, waardoor er een kleinere hoeveelheid ruimte beschikbaar is voor de ademhaling. Naast de hyperinflatie die zittend in rust gemeten wordt (statische hyperinflatie), bestaat er ook ‘dynamische’ hyperinflatie. Dynamische hyperinflatie wordt vaak uitgelokt door inspanning. De ademfrequentie neemt toe bij inspanning, waardoor er minder tijd beschikbaar is per in- en uitademing. Doordat de uitademing bemoeilijkt is door de luchtwegvernauwing bij COPD, blijft er bij een snelle ademhaling onvoldoende tijd over om volledig uit te ademen. Hierdoor stapelt de lucht zich op in de longen, en blijft er nog minder ruimte over voor de ademteugen, waardoor kortademigheid ontstaat.

Om te beoordelen of er sprake is van een luchtwegvernauwing en/of statische hyperinflatie wordt longfunctieonderzoek gebruikt.

Bij een spirometrie wordt het volume en de stroomsnelheid van de lucht gemeten tijdens een krachtige uitademing. Hierbij wordt zowel het volume van de totale uitgeademde lucht gemeten (‘forced vital capacity’, FVC) als ook het volume van de lucht die wordt uitgeademd tijdens de eerste seconde (‘forced expiratory volume in 1 second’, $FEV_1$). De $FEV_1$/FVC ratio

wordt gebruikt om te beoordelen of er sprake is van een luchtwegvernauwing. De hoogte van de $FEV_1$ wordt gebruikt om de ernst van de luchtwegvernauwing in te schatten. Zo wordt een $FEV_1$ van 30-50% van voorspeld ingeschat als matig-ernstig en een $FEV_1$ <30% van voorspeld als een ernstige luchtwegvernauwing. In de voorspelde waardes voor de longfunctie zitten verschillen op basis van leeftijd, lengte, geslacht en etniciteit.

Bij een volumemeting van de longen wordt onder meer de longinhoud bij maximale inademing (totale longcapaciteit, TLC) en na maximale uitademing (residuaal volume, RV) bepaald. De hoogte van het RV en de RV/TLC ratio zijn twee belangrijke maten voor de aanwezigheid en ernst van de statische hyperinflatie.

De ernst van COPD wordt vastgesteld op basis van de ernst van de luchtwegvernauwing, het aantal longaanvallen en de klachten die de patiënt ervaart. Andere kenmerken die geassocieerd zijn met ernstiger vormen van COPD en een hogere kans op overlijden zijn de aanwezigheid van een te laag zuurstof- of te hoog koolzuurgehalte in het bloed, een hoge bloeddruk in de longvaten (pulmonale hypertensie), ernstige hyperinflatie, ondergewicht en de aanwezigheid van meerdere andere ziektes.

COPD is niet te genezen, maar er zijn wel diverse behandelopties. Het lastige hierbij is echter dat COPD een heterogene aandoening is, wat betekent dat de ziekte zich bij verschillende patiënten op verschillende manieren kan uiten. Hierdoor zijn niet alle behandelingen geschikt voor iedere patiënt, en moet op individuele basis gekeken worden welke opties er zijn. Stoppen met roken is essentieel om het ziektebeloop te vertragen. Andere belangrijke niet-medicamenteuze opties zijn voorlichting over de aandoening, begeleiding bij onder- of overgewicht en fysiotherapie voor training en ademhalingstechnieken. De hoeksteen van de medicamenteuze behandeling zijn inhalatoren met langwerkende luchtwegverwijders. Als er regelmatig longaanvallen voorkomen wordt daarnaast vaak ook een inhalatiecorticosteroïd voorgeschreven, dit middel heeft een ontstekingsremmend effect.

## Longvolumereductie behandeling

Longvolumereductie behandelingen zijn ontwikkeld voor patiënten met COPD die emfyseem hebben en daardoor ernstige hyperinflatie. Doel van deze behandelingen is om de hyperinflatie te verminderen, wat leidt tot afname van kortademigheid, een beter inspanningsvermogen en een betere kwaliteit van leven.

Chirurgische longvolumereductie is de oudste vorm van dit type behandelingen, en bestaat al sinds de jaren vijftig van de vorige eeuw. Bij klassieke longvolumereductie chirurgie wordt van één of beide longen een stuk weefsel met veel emfyseem verwijderd, zodat de betere longdelen meer ruimte krijgen. Een andere vorm van longvolumereductie chirurgie is het verwijderen van een hele longkwab met veel emfyseem via een kijkoperatie.

Omdat een longoperatie een ingrijpende procedure is voor kwetsbare patiënten met ernstig COPD, zijn er in de afgelopen twee decennia bronchoscopische longvolumereductie behandelingen ontwikkeld. Een bronchoscoop heeft een dunne, makkelijk buigzame slang met op het uiteinde een camera. Deze kan via de mond, neus of of via een beademingsbuisje opgevoerd worden tot in de luchtwegen. Ook loopt er een werkkanaal in de slang, wat de mogelijkheid geeft om een behandeling uit te voeren. Behandeling met éénrichtingsventielen en coils zijn de twee bekendste vormen van bronchoscopische longvolumereductie behandeling, die beiden ook benoemd worden als behandeloptie bij COPD in de internationale richtlijnen. De behandeling met éénrichtingsventielen wordt sinds 2017 ook vergoed door de zorgverzekering in Nederland. Van beide behandelingen is aangetoond met wetenschappelijk onderzoek dat ze een positief effect hebben op hyperinflatie, luchtwegvernauwing, inspanningsvermogen en kwaliteit van leven.

Eénrichtingsventielen worden geplaatst in de luchtwegen van de longkwab die het meeste is beschadigd door emfyseem. Hierdoor kan er geen lucht meer ín de longkwab stromen, terwijl de aanwezige lucht in de longkwab er wel uit kan stromen. Het doel hiervan is het volume van de longkwab te verkleinen, zodat de hyperinflatie afneemt. Om een effectieve ventielbehandeling uit te kunnen voeren is het heel belangrijk dat er geen open verbinding is tussen de longkwab die behandeld wordt en de andere longkwab(ben), zogenaamde collaterale ventilatie. In dat geval blijft er namelijk ondanks de eenrichtingsventielen continu lucht in de longkwab stromen en wordt deze niet of nauwelijks kleiner.

Bij behandeling met coils worden de twee longkwabben met het meest uitgesproken emfyseem behandeld. Het doel is hierbij niet om longkwab volledig af te sluiten, en de aanwezigheid van collaterale ventilatie vormt daarom ook geen belemmering voor de behandeling. De coils zijn hele dunne draadjes van geheugenmetaal die zich opkrullen in het longweefsel. Dit zorgt voor een versteviging van het uitgerekte, emfysemateuze longweefsel en zorgt op deze wijze voor longvolumereductie. Er worden per longkwab 10-12 coils geplaatst in de luchtwegen.

## Dit proefschrift

Dit proefschrift had twee doelstellingen. Ten eerste het vergroten van de kennis over het werkingsmechanisme van longvolumereductie behandelingen. Dit ter verbetering en waar mogelijk uitbreiding van patiëntenselectie en om een optimale afweging te kunnen maken tussen de kans op een succesvolle behandeling en de kans op complicaties. De tweede doelstelling van dit proefschrift was het verbeteren van de behandeling van hardnekkige kortademigheid bij COPD door het effect van laag gedoseerde opioïden te onderzoeken.

In **hoofdstuk 2** beschrijven we behandelopties voor patiënten met ernstig COPD. Zoals hierboven benoemd kan COPD zich verschillend uiten bij verschillende patiënten, de ziekte heeft dus niet bij iedereen dezelfde kenmerken. In dit hoofdstuk proberen we

ons te richten op de zogenaamde ‘behandelbare kenmerken’: die kenmerken waar een behandeling voor beschikbaar is. Voorbeelden van behandelbare kenmerken bij COPD zijn de aanwezigheid van hyperinflatie, frequente longaanvallen en een verhoogd koolzuur in het bloed. Behandelingen die besproken worden in dit hoofdstuk zijn onder meer de bronchoscopische longvolumereductie opties, het nachtelijk gebruik van een beademingskap (non-invasieve ventilatie), longrevalidatie en longtransplantatie. Aan de hand van een patiëntenbeschrijving wordt besproken op welke manier zorg en diagnostiek kan worden aangeboden aan patiënten met ernstig COPD zodat er een gepersonaliseerde behandeling kan worden gegeven.

In **hoofdstuk 3** hebben we een analyse verricht van de wetenschappelijke literatuur over verandering in gaswisseling en diffusiecapaciteit door behandeling met éénrichtingsventielen of longvolumereductie chirurgie. Met gaswisseling wordt de opname van zuurstof van de longen naar het bloed en de uitscheiding van koolzuur van het bloed naar de longen bedoeld. Het transport van zuurstof en koolzuur over de wand van een longblaasje en de wand van het bloedvat wordt diffusie genoemd, dit is een passief proces op basis van drukverschillen. Door een deel van het longweefsel te verwijderen (chirurgie) of af te sluiten (met éénrichtingsventielen) neemt het gaswisselingsoppervlakte af. Op basis hiervan zou de verwachting kunnen zijn dat de diffusiecapaciteit en gaswisseling verslechteren door deze behandelingen. Uit de analyse blijkt echter dat de diffusiecapaciteit juist significant verbetert. De gaswisseling blijft nagenoeg gelijk. We bespreken in dit hoofdstuk de mogelijke mechanismes hiervoor. Verbetering in de gelijkmatigheid waarmee de lucht zich over de longen verspreidt en een verbeterde verhouding tussen ventilatie (luchtverplaatsing in de longen) en doorbloeding van de longen na longvolumereductie behandeling zijn aannemelijke verklaringen hiervoor. Omdat de diffusiemeting bij COPD beïnvloed wordt door meerdere factoren, zoals ongelijkmatige ventilatie en een luchtwegobstructie, bespreken we tot slot ook nog of er alternatieve opties zijn om de diffusiecapaciteit betrouwbaarder te meten.

Patiënten met een hele lage diffusiecapaciteit (20% of lager van de voorspelde waarde) zijn vaak uitgesloten van deelname aan wetenschappelijk onderzoek naar behandeling met éénrichtingsventielen. Dit komt doordat in een groot wetenschappelijk onderzoek naar longvolumereductie chirurgie (de zogeheten NETT trial) patiënten met onder meer een diffusiecapaciteit ≤20% een hoger risico hadden om te overlijden na de operatie. In **hoofdstuk 4** hebben we terugkijkend onderzocht of de veiligheid en het effect van de ventielbehandeling bij patiënten met een diffusiecapaciteit ≤20% vergelijkbaar is met patiënten die een hogere diffusiecapaciteit hebben. In beide groepen werden 20 patiënten geïncludeerd in de analyse, waarbij er op gelet is dat zij vergelijkbaar waren qua leeftijd, geslacht, ernst van de luchtwegvernauwing en hyperinflatie. De groep met een lage diffusiecapaciteit had een significante verbetering in luchtwegvernauwing, hyperinflatie, loopafstand en kwaliteit van leven zes maanden na de ventielbehandeling. Geen van de patiënten is in deze periode overleden. Een klaplong (pneumothorax) was de

complicatie die het vaakste voorkwam, in 15% van de patiënten. Dit was goed oplosbaar met standaardbehandeling. Er waren geen significante verschillen in de uitkomst van de patiëntengroep met een diffusiecapaciteit ≤20% ten opzichte van de groep met een diffusiecapaciteit>20%. Ook waren de uitkomsten vergelijkbaar met die van eerdere publicaties over ventielbehandeling. Al met al hebben we geconcludeerd dat behandeling met ventielen bij patiënten met COPD en een diffusiecapaciteit ≤20% effectief en veilig kan zijn.

Van statische hyperinflatie is bekend dat dit afneemt na bronchoscopische longvolume-reductie, maar het effect op dynamische hyperinflatie is minder goed onderzocht. In **hoofdstuk 5** beschrijven we een prospectieve cohort studie uitgevoerd in het UMCG waarbij verandering in dynamische hyperinflatie na bronchoscopische longvolumereductie werd vergeleken met standaardzorg. Dynamische hyperinflatie werd uitgelokt door een 'manually paced tachypnea' (MPT) test, waarbij deelnemers geïnstrueerd werden met tussenpozen driemaal een minuut snel te ademen (40x/min). Voor en na de snelle ademhaling werd telkens een meting van de inspiratoire capaciteit (aantal liters lucht dat maximaal ingeademd kan worden na een rustige uitademing) uitgevoerd. Dynamische hyperinflatie werd gedefinieerd als de daling van de inspiratoire capaciteit na de test. De meting werden uitgevoerd voorafgaand en 6 maanden na bronchoscopische longvolumereductie behandeling met éénrichtingsventielen of coils (behandelgroep) of standaardzorg (controlegroep). De behandelgroep bestond uit achttien patiënten, de controlegroep bestond uit dertien patiënten. De mediane verandering in dynamische hyperinflatie in de behandelgroep was +225 ml (van − 113 tot +803ml, $p$<0.01) ten opzichte van 0 ml (van −1067 tot +500, p=0.42) in de controlegroep. Het verschil tussen de groepen was statistisch significant (p<0.01). Er was een significante associatie tussen toename van dynamische hyperinflatie en afname van het residuale volume (r = − 0.439, $p$ < 0.01). Onze conclusie van deze studie was dat bronchoscopische longvolumereductie behandeling het vermogen tot dynamische hyperinflatie doet toenemen, meest waarschijnlijk doordat de statische hyperinflatie is afgenomen.

In **hoofdstuk 6** beschrijven we een prospectieve studie uitgevoerd in het UMCG waarbij een vergelijking werd gemaakt tussen dynamische hyperinflatie gemeten bij drie verschillende onderzoeken: de fietsergometrie (de gouden standaard), de zes-minuten looptest, en de 'manually paced tachypnea' test (MPT). Er werden 29 patiënten met ernstig COPD geïncludeerd in de studie, die voor en na bronchoscopische longvolumereductie behandeling met endobronchiale coils deze metingen ondergingen. Er was geen significante verandering in dynamische hyperinflatie na behandeling met coils. Vergelijking van de dynamische hyperinflatie gemeten met de fietstest en de MPT liet een sterke associatie zien (rho 0.660, p < 0.001) maar met een matige overeenkomst (Bland Altman plot, 202 ml verschil, waarbij de MPT gemiddeld hoger uitvalt). Er was een matige associatie tussen dynamische hyperinflatie gemeten met de fietsergometrie en zes-minuten looptest (rho 0.361, p=0.024). Uit de resultaten van dit hoofdstuk concludeerden we dat de MPT test

een geschikt alternatief kan zijn voor een fietsergometrie om dynamische hyperinflatie te meten bij ernstig COPD, maar dat dynamische hyperinflatie mogelijk wel overschat wordt. Een verklaring hiervoor zou kunnen zijn dat de ademhalingssnelheid hoger is bij de MPT vergeleken met de fietsergometrie.

In **hoofdstuk 7** werd de bruikbaarheid, veiligheid en effectiviteit van een nieuwe maat éénrichtingsventiel (maat 5.5-'Low Profile (LP)' met een kortere lengte dan maat 5.5) onderzocht in een prospectieve open-label studie in het UMCG. Deze ventielmaat is ontworpen voor luchtwegen die relatief wijd en kort zijn. Er werden 30 patiënten geïncludeerd waar tenminste 1 éénrichtingsventiel in de maat 5.5LP werd geplaatst tijdens bronchoscopie. Er was tijdens deze procedures geen herplaatsing van een 5.5LP ventiel noodzakelijk. Eén patiënt ontwikkelde een asymptomatische klaplong na de behandeling. Bij vier patiënten was een nieuwe bronchoscopie nodig vanwege onvoldoende effect van de behandeling, bij 1 procedure bleek dit te liggen aan een verplaatsing van het 5.5LP ventiel. Er was een statistisch en klinisch significant effect op afname van het volume van de behandelde longkwab, $FEV_1$, residuaal volume en kwaliteit van leven. We concludeerden dat het plaatsen van een 5.5LP ventiel niet gepaard ging met onverwachte complicaties en dat er een goed longvolumereductie effect bereikt kon worden.

De meest voorkomende bijwerking van bronchoscopische longvolumereductie behandeling met éénrichtingsventielen is een klaplong (pneumothorax), wat voorkomt bij tot 34% van de behandelde patiënten. Omdat de klaplong meestal goed op te lossen is, en de winst wat betreft kortademigheid, inspanningsvermogen en kwaliteit van leven van de ventielbehandeling groot kan zijn, wordt dit risico als acceptabel ingeschat. Wel is het van belang om in klinieken waar de ventielbehandeling wordt uitgevoerd een team te hebben dat bedreven is in het herkennen en adequaat behandelen van een pneumothorax bij patiënten met ernstig COPD. In **hoofdstuk 8** beschrijven we een praktische aanbeveling voor de behandeling van een pneumothorax na ventielbehandeling. Ook worden ontstaansmechanismes, risicofactoren en preventie van een pneumothorax post-ventielbehandeling besproken. De aanbeveling is een update van de aanbeveling uit 2014. De aanbeveling is opgesteld aan de hand van de beschikbare wetenschappelijke literatuur en met behulp van een gemodificeerde Delphi methode, met als doel consensus te verkrijgen over onderwerpen waar nog onvoldoende wetenschappelijke literatuur beschikbaar is. Hiervoor kreeg een expert panel van negen longartsen gespecialiseerd in bronchoscopische interventies in drie rondes vragen over dit onderwerp voorgelegd.

Hardnekkige kortademigheid is de meest voorkomende klacht bij ernstig COPD. Het betreft kortademigheid die blijft bestaan ondanks optimale standaardbehandeling en dit komt voor bij bijna alle patiënten met ernstig COPD in hun laatste levensjaar. Een mogelijke medicamenteuze optie voor moeilijk behandelbare kortademigheid is een lage dosis opioïden (morfine en vergelijkbare middelen). Onze studie MoreFoRCOPD (Morphine or Fentanyl for Refractory Dyspnea in COPD) onderzoekt het effect van twee soorten

opioïden in lage dosis op hardnekkige kortademigheid bij COPD. Aanvankelijk was het de bedoeling de resultaten van deze studie te beschrijven in **hoofdstuk 9**. Echter, door grote vertraging ten gevolge van de Corona-pandemie, hebben we er in plaats daarvan voor gekozen in dit hoofdstuk onze onderzoeksopzet te beschrijven, gecombineerd met een systematische evaluatie van de literatuur. Voor de systematische literatuur-evaluatie werd gerandomiseerd, placebo-gecontroleerd klinisch onderzoek geïncludeerd waarbij opioïden werden voorgeschreven voor hardnekkige kortademigheid bij COPD. Alleen onderzoeken waarbij informatie werd gegeven over het effect van de behandeling op kortademigheid, gezondheidsstatus of kwaliteit van leven werden meegenomen in de analyse. Vijftien onderzoeken beschreven kortademigheid als uitkomstmaat, in drie onderzoeken was er een statistisch significant positief effect op kortademigheid. Slechts één van de vier onderzoeken waar informatie werd verstrekt over kwaliteit van leven of gezondheidsstatus beschreef een significant positief effect op deze uitkomstmaat. In twee-derde van de geïncludeerde onderzoeken werd morfine onderzocht. Er waren geen placebo-gecontroleerde onderzoeken naar fentanyl. De hypothese van onze studie is dat fentanyl en morfine allebei beter werken tegen hardnekkige kortademigheid dan placebo, en dat fentanyl minder bijwerkingen geeft dan morfine. Hiervoor hebben we een dubbelblinde, cross-over, gerandomiseerde, placebo-gecontroleerde studie in tien ziekenhuizen ontworpen met drie behandelarmen (fentanylpleister met placebocapsules, morfinecapsules met placebopleister en placebopleister met placebocapsules). De fentanylpleister wordt voorgeschreven in een dosering van 12 mcg/uur, de morfinecapsules met gereguleerde afgifte tweemaal daags 10 mg. Primair eindpunt van de studie is verandering in dagelijkse gemiddelde kortademigheid gemeten op een schaal van 0 tot 10. Verder wordt informatie verzameld over de ergste kortademigheid per dag, kwaliteit van leven, slaapkwaliteit, hypercapnie (verhoogde koolzuurspiegel), bijwerkingen en voorkeur van de patiënt. In totaal zullen zestig patiënten met ernstig COPD en hardnekkige kortademigheid (Gold klasse III of IV, mMRC kortademigheidsscore ≥3, optimale standaardbehandeling) worden geïncludeerd. Per 11-07-2022 zijn 41 patiënten in de studie geïncludeerd, in totaal zullen 60 patienten deelnemen aan de studie.

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Lieve Fieke en Joost, de totstandkoming van dit proefschrift is als het goed is grotendeels langs jullie heen gegaan. Maar ik wil jullie toch heel graag hier noemen. want ik hou van jullie en geniet er van om jullie te zien opgroeien.

# Curriculum Vitae

Marlies van Dijk werd in 1985 geboren te Bolsward. In 2003 rondde zij cum laude het VWO af aan het Marne College in Bolsward en startte zij met haar geneeskundestudie aan de Rijksuniversiteit te Groningen. Na het afronden van haar studie in 2010, met onder meer co-schappen in het UMC Groningen, Wilhelmina ziekenhuis te Assen en Scheper ziekenhuis in Emmen, startte zij met de opleiding tot longarts. De vooropleiding vond plaats in het Martini Ziekenhuis. Daarna volgden vier opleidingsjaren in het UMC Groningen, met in het laatste jaar van de opleiding verdieping op het gebied van longrevalidatie en ernstig astma (in het Medisch Centrum Leeuwarden).

In 2017 rondde Marlies haar opleiding tot longarts af. Zij startte met een fellowship 'Ernstig COPD en bronchoscopische interventies', waar dit proefschrift onderdeel van is. In 2019 werd het fellowship omgezet naar een vaste stafaanstelling. Haar aandachtsgebieden zijn ernstig COPD en bronchoscopische interventies. Daarnaast is zij medisch hoofd van het functiecentrum longfunctie en allergologie.

Marlies woont in Groningen met haar partner Laurin Thole en hun kinderen Fieke en Joost.

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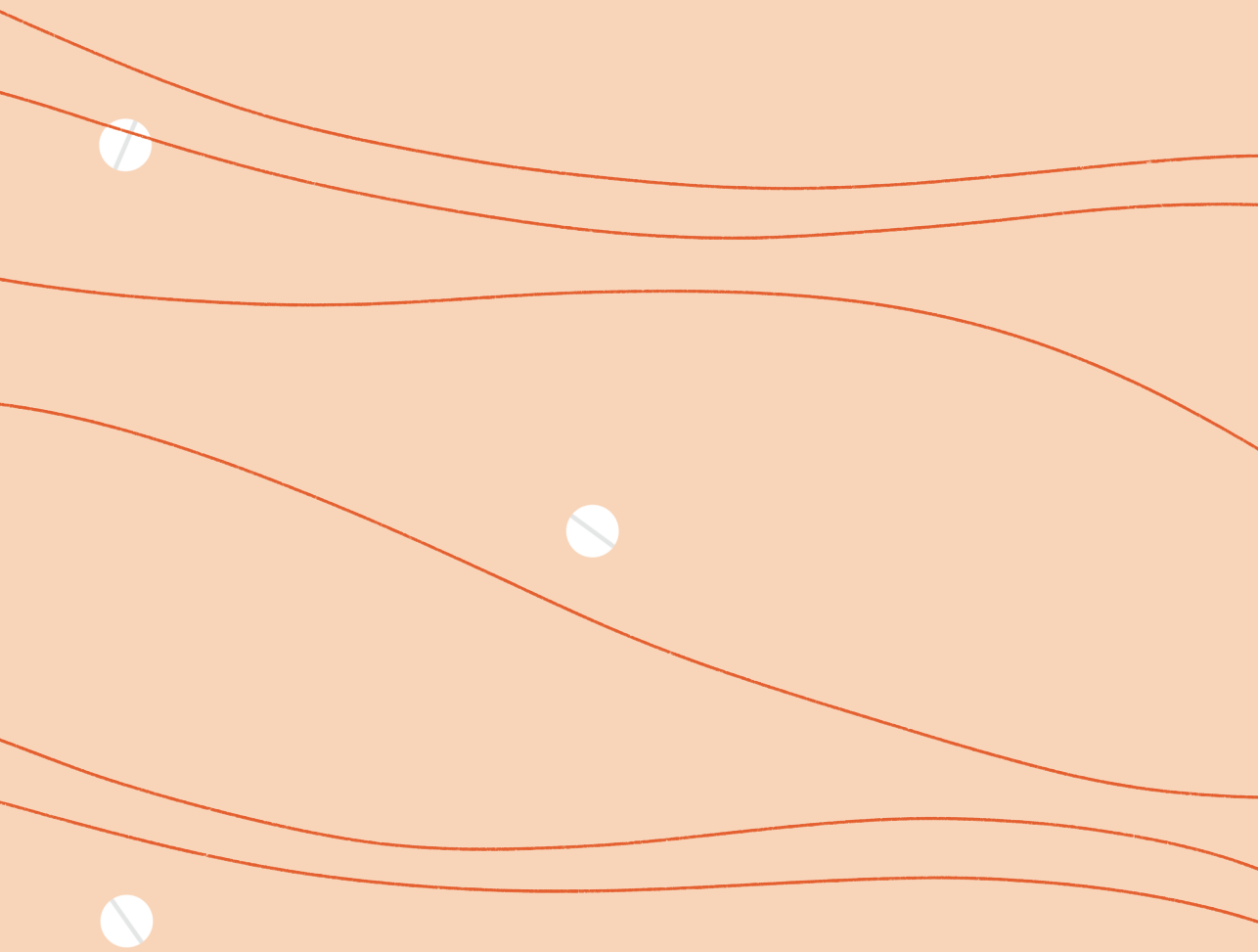

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