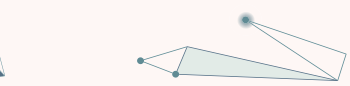
CHAPTER

1

General introduction



GENERAL INTRODUCTION

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a complex and heterogeneous condition characterized by persistent and often progressive airflow limitation, chronic respiratory symptoms, and structural changes to the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) [1-4]. COPD has a profound impact worldwide, affecting an estimated 200 million individuals and ranking among the top three leading causes of death [5]. The development of COPD is the result of complex interactions between various risk factors, including exposure to inhaled particular matter such as cigarette smoke and air pollutants, genetic susceptibility, developmental factors, and a low socioeconomic status [1, 3, 4, 6].

Dyspnoea is the hallmark symptom of COPD and a major cause for the disability and anxiety associated with the disease [4, 7]. In addition to dyspnoea, several other symptoms may be present, such as cough, sputum production, wheezing, and chest tightness [4, 7]. Each of these symptoms can have a profound effect on the individual's quality of life, overall health and functional status.

Several pharmacological and non-pharmacological therapies are available for COPD, including bronchodilators, oxygen therapy, physical therapy, pulmonary rehabilitation, and interventional or surgical approaches such as lung transplantation and lung volume reduction treatments [4]. The approach to treating a patient with COPD should be personalised, tailoring interventions based on the identification of their treatable traits [4, 8]. This involves a consideration of the predominant symptoms alongside the endotype and phenotype of the disease. Particularly, one of the most important treatable traits in COPD is the presence of substantial hyperinflation.

Hyperinflation

Hyperinflation of the lung is defined as an increase in the end-expiratory volume relative to that of healthy individuals and can be subdivided into static and dynamic hyperinflation (figure 1) [9-11]. Some degree of hyperinflation is encountered in the majority of COPD patients, although it is especially prevalent in patients with a predominant emphysematous phenotype. Emphysema is pathologically defined as an abnormal and permanent enlargement of the air spaces distal to the terminal bronchioles with destruction of alveolar walls [12]. The associated loss of elastic tissue reduces the elastic recoil pressure of the lungs, allowing premature airway collapse during expiration and subsequently leads to air trapping and static lung hyperinflation [9, 10]. Dynamic hyperinflation, a temporary increase in end-expiratory volume during exercise, occurs on top of the pre-existing static hyperinflation. The elevate ventilatory demand during exercise, requiring a higher respiratory rate, in combination with the present airflow limitation causes the next breath to be initiated before full expiration. This results in progressive air trapping, ultimately limiting exercise capacity [9, 13]. While the assessment of airflow obstruction is essential for the diagnosis and staging of COPD, the

presence and severity of hyperinflation are more closely associated with symptoms and level of functional impairment in patients with moderate-to-severe COPD [4, 10, 14, 15].

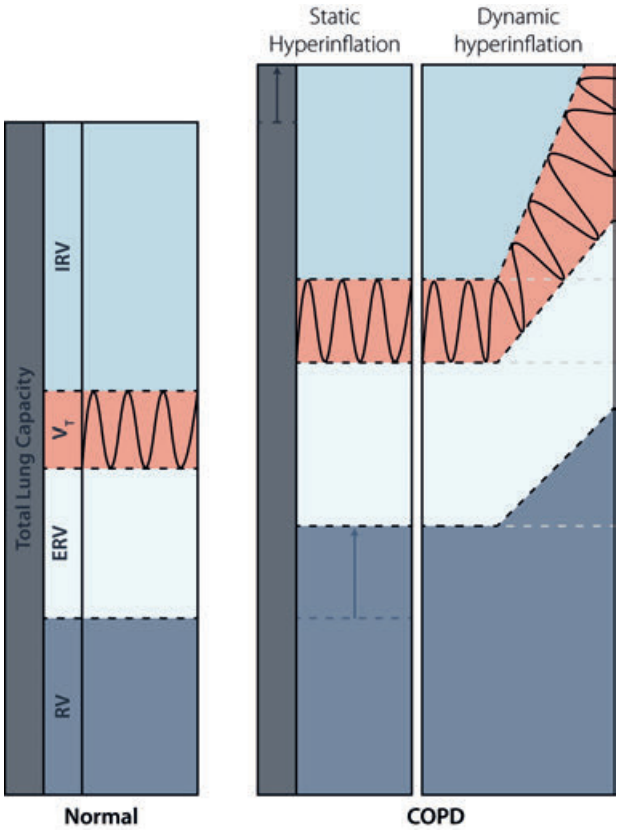


Figure 1. Lung volumes in healthy subjects, during rest, and in patients with chronic obstructive pulmonary disease (COPD) during rest and exercise. Static hyperinflation is characterised by an increase in total lung capacity but more pronounced in residual volume, resulting in a higher end-expiratory volume compared to healthy individuals. Dynamic hyperinflation is a temporary increase in end-expiratory volume during exercise which ultimately impairs exercise capacity. IRV = inspiratory reserve volume; VT = tidal volume; ERV = expiratory reserve volume; RV = residual volume.

Lung volume reduction treatment

For a subset of COPD patients, characterized by advanced emphysema and severe static hyperinflation, lung volume reduction can be a beneficial treatment option. Lung volume reduction reduces air trapping and hyperinflation, thereby enhancing the mechanics of the respiratory muscles by restoring a more physiological configuration and restoring some of the elastic recoil pressure [16]. Additionally, it is suggested that lung volume reduction decreases ventilation and perfusion heterogeneity, subsequently improving alveolar gas exchange and ventilation efficiency [16]. These positive effects are often reflected by improvements

in pulmonary function, exercise capacity, and quality of life, and may even contribute to a survival benefit [16, 17].

The first developed lung volume reduction approach was lung volume reduction surgery (LVRS). The largest randomized controlled trial comparing LVRS to standard medical care (National Emphysema Treatment Trial) demonstrated the efficacy of LVRS in patients with upper lobe-predominant heterogeneous emphysema and low baseline exercise capacity [18]. However, for patients with other characteristics, LVRS could be associated with a higher risk of post-operative mortality or yield no substantial treatment benefit [16, 18]. Initial concerns over the LVRS-associated mortality and morbidity drove the development of less invasive bronchoscopic lung volume reduction techniques, including one-way endobronchial valves, lung volume reduction coils, lung sealants, thermal vapor ablation, and the airway bypass [19-21]. Among these options, endobronchial valves and coils have been the most extensively studied and both have been included in COPD treatment guidelines [4]. However, endobronchial valves are currently the only bronchoscopic lung volume reduction option that is accepted as a routine care treatment in the Netherlands.

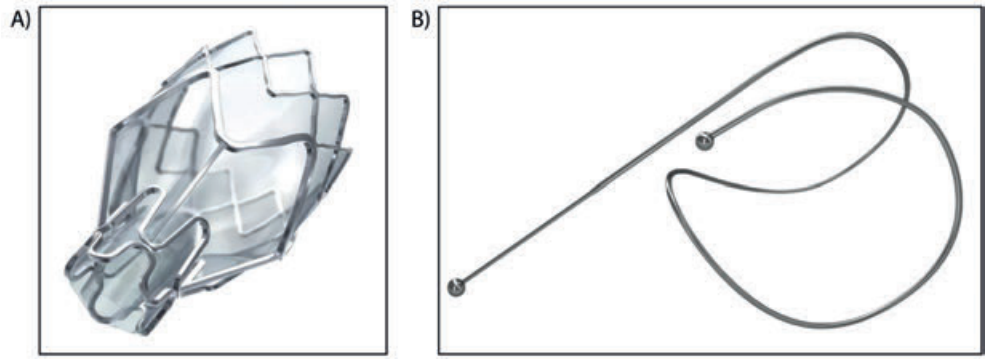


Figure 2. Lung volume reduction devices. A) Zephyr Endobronchial Valve and B) Repneu Coil.

One-way endobronchial valves

Bronchoscopic lung volume reduction using one-way endobronchial valves (figure 2A) has been designed to mimic the effect of LVRS by unilaterally targeting the lobe most affected by emphysema. Endobronchial valves are implanted in all (sub-) segmental bronchi of a targeted lobe with the objective to induce a complete lobar atelectasis [22, 23]. The unidirectional mechanism of the valves allows the exit of air from the targeted lobe while obstructing the entry of air, leading to deflation of the treated lobe. For this to work, absence of collateral ventilation between the targeted and ipsilateral nontargeted lobe(s) is crucial, and requires the presence of (almost) complete interlobar fissures [24]. Fissure integrity is initially assessed through visual inspection and quantitative examination of a computed tomography (CT) scan [22, 23]. Before definite implantation of the valves, the absence of collateral ventilation can be confirmed by a bronchoscopic Chartis measurement which is performed during the same procedure [25, 26].

In addition to absence of collateral ventilation, patients must fulfil other criteria to be eligible for endobronchial valve treatment. Potential treatment candidates should be on optimal medical treatment yet remain highly symptomatic with low exercise performance [22, 23]. Furthermore, these limitations should predominantly arise from the presence of substantial hyperinflation. To identify patients with substantial hyperinflation, the selection criteria of most clinical trials included a residual volume of at least 175% of predicted and a residual volume over total lung capacity ratio of at least 55%. Nevertheless, evidence suggests that patients with less severe hyperinflation can also benefit from endobronchial valve treatment if there is a pronounced treatment target [27]. The selection criteria for endobronchial valve treatment have not been extensively studied but are a topic of interest. Despite meeting the current eligibility criteria and undergoing a technically successful procedure, a number of patients experience no meaningful benefit, indicating a potential oversight of certain criteria or that some are not given sufficient weight in the decision process. Furthermore, some of the selection criteria are subject of ongoing discussion, such as the eligibility of a patient with a homogeneous distribution of emphysema.

Overall, clinical trials have shown that, in adequately selected patients, endobronchial valve treatment leads to significant and clinically meaningful improvements in pulmonary function, exercise capacity, and quality of life [24, 28-31]. While the treatment effect shows a gradual decline over time, likely due to the progressive nature of COPD, a substantial treatment effect can persists for at least three years post-treatment [32]. Despite best efforts, some patients experience a lack of treatment benefit, while others lose their initial treatment effect, and some encounter complications directly related to the treatment or the device, such as pneumothorax, pneumonia, acute exacerbation of COPD, or the formation of granulation tissue [33]. The occurrence of these complications can require a follow-up bronchoscopy for inspection, adjustments or replacement, or, in some cases, complete removal of the implanted valves [33]. While revision bronchoscopies following endobronchial valve treatment are recommended for specific indications by experts [23] and are routinely performed, there is limited knowledge regarding their incidence, indications, and outcomes. Furthermore, the frequent observation of granulation tissue formation during these revision bronchoscopies, which is a known complication from other lung-implantable devices such as airway stents, is not fully understood regarding the underlying biological mechanisms, causes, and risk factors.

Lung volume reduction coils

Lung volume reduction coils (figure 2B) are shape-memory nitinol implants that, in contrast to endobronchial valves, do not require fissure integrity and do not induce a lobar atelectasis. Coils are implanted in all sub-segmental airways of the two (contralateral) lobes most destructed by emphysema. While their precise mechanism of action remains incompletely understood, it is suggested to involve a dual process: reduction of lung volume through compression of diseased tissue and the restoration of some elastic properties of the lung, thereby enhancing the elastic recoil of the lung and improving airway tethering [19, 34].

The criteria for eligibility are similar to those for endobronchial valve treatment, except for the fissure integrity requirement. Additionally, patients with symptoms indicating concurrent airway disease, such as frequent COPD exacerbations or recurrent respiratory infections, should not be considered for coil treatment [34]. The implantation of any device in the airways can exacerbate these respiratory adverse events, and unlike endobronchial valves that can be removed if needed, coil implantation is permanent.

Clinical trials have demonstrated a positive effect of coil treatment on pulmonary function, quality of life, and, to a lesser extent, on exercise capacity compared to standard medical care [35-38]. However, response variability was substantial and only approximately 50-60% of patients deemed responders on pulmonary function or exercise capacity outcomes [35-38]. Subsequent investigations indicated that targeting the two lobes most severely affected by emphysema based on quantitative CT analysis (with a minimum destruction of 20% at -950 Hounsfield Units) and substantial hyperinflation (residual volume exceeding 200% of predicted) were important predictors for a positive treatment response [37, 39, 40]. The ELEVATE trial was designed to explore whether incorporating these identified predictors into the selection criteria would enhance treatment effectiveness and responder rates [41]. Unfortunately, during the trial, the company responsible for producing the lung volume reduction coil decided to stop production. This decision resulted in premature termination of the study and cessation of further treatment of patients with this coil, both within and outside the context of a clinical trial [36]. This discontinuation combined with the potential of bronchoscopic lung volume reduction coil treatment drove the development of newer generation coils. Future trial are needed to investigate their safety and efficacy.

Outline of this thesis

This thesis aims to broaden the knowledge on bronchoscopic lung volume reduction, exploring various facets from advancing patient selection, exploring the granulation tissue response, and examining the safety and efficacy of a new (second generation) coil as a bronchoscopic lung volume reduction option. The goal is to improve efficacy and longevity of endobronchial valve treatment and broaden the therapeutic options for patients with advanced emphysema limited other treatment options.

Chapter 2 focuses on the essential role of adequate sedation during bronchoscopic lung volume reduction procedures, detailing the anaesthetic management techniques and mechanical ventilation settings used during these procedures in our treatment center. Furthermore, the chapter evaluates the frequency, severity, and types of anaesthesia-related adverse events encountered during bronchoscopic lung volume reduction procedures.

In **chapter 3** we compare residual volume reference values derived from the 1993-European Community for Steel and Coal equation, a widely used standard until recently, with those derived from the 2020-Global Lung Function Initiative equation, the current standard. Based on this comparison, we propose a new cut-off value for residual volume that can be used in

the context of patient selection for bronchoscopic lung volume reduction treatments.

In **chapter 4** we explore the long-term survival outcomes after endobronchial valve treatment and examen whether treatment response, as measured by various endpoints, contributes to a survival benefit for these patients.

Chapter 5 and 6 focus on identifying predictors of response to endobronchial valve treatment. Understanding which and to what extent pretreatment characteristics influence response to treatment is crucial to improve treatment outcomes and select the patients which are expected to experience a meaningful treatment benefit. **Chapter 5** specifically explores the impact of emphysema distribution on treatment response, a widely discussed characteristics in the context of patient selection. In **chapter 6**, a cluster analysis is conducted to identify responder and nonresponder clusters and compare characteristics in order to identify which are most important for a favourable treatment outcome.

Chapter 7, 8 and 9 focus on revision bronchoscopies and granulation tissue formation after endobronchial valve treatment. Revision bronchoscopies can be necessary to get a sustained treatment effect or to address complications. **Chapter 7** outlines the frequency and indications for these revision bronchoscopies and the observations and interventions during this bronchoscopy. Granulation tissue formation is a common complication after endobronchial valve treatment and is a concern encountered with various other lung implantable devices. In **chapter 8** we review existing literature on potential risk factors for granulation tissue development after treatment with lung implantable devices. Additionally, **chapter 9** evaluated the hypothesis that inaccurate sizing of the endobronchial valve to the airway diameter might contribute to granulation tissue formation.

In **chapter 10** we evaluate the concern of nickel release from endobronchial valves, which are consist of a nitinol (alloy of nickel and titanium) frame covered by a silicone layer, the presence of nickel hypersensitivity is a relative contraindication. With the high prevalence of nickel hypersensitivity worldwide, we compared the nickel concentration in lung tissue of a patient previously treated with endobronchial valves to a control sample.

Chapter 11 and 12 focus on bronchoscopic lung volume reduction using coils. In **chapter 11** we systematically review the existing literate to identify all clinical trials using the initially developed lung volume reduction coil and perform a meta-analysis using individual participant data to give an overall treatment effect up to 12 months after treatment. **Chapter 12** describes the first inhuman study using the newly developed second generation coil and present the results on safety, feasibility and efficacy.