Bronchoscopic lung volume reduction

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CHAPTER

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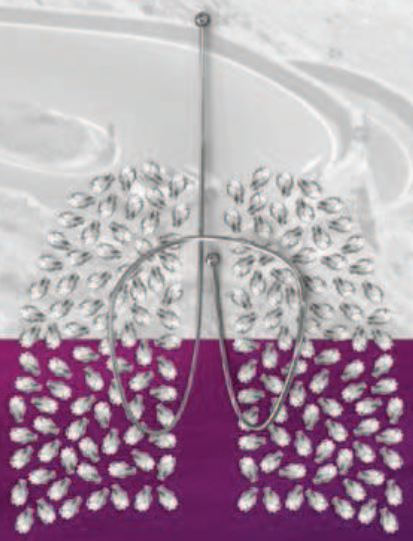


General introduction

GENERAL INTRODUCTION

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

COPD

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

Prevalence of COPD

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

Symptoms and health related quality of life

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

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

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

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

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

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

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

The GOLD classification of combined COPD assessment.

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

Available treatments for patients with COPD

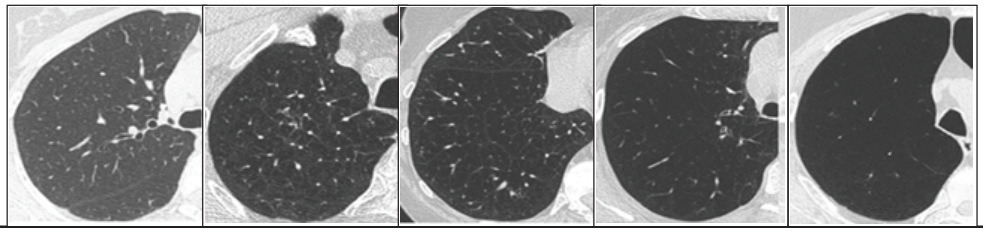
To date, there is not one single treatment available that will cure COPD. Currently, smoking cessation is the only treatment that has been demonstrated to slow down the accelerated decline in lung function in COPD, independent of previous heavy smoking, advanced age or poor baseline lung function.[14]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

Emphysema phenotypes

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

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

Overview of a quantitative emphysema score

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

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

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

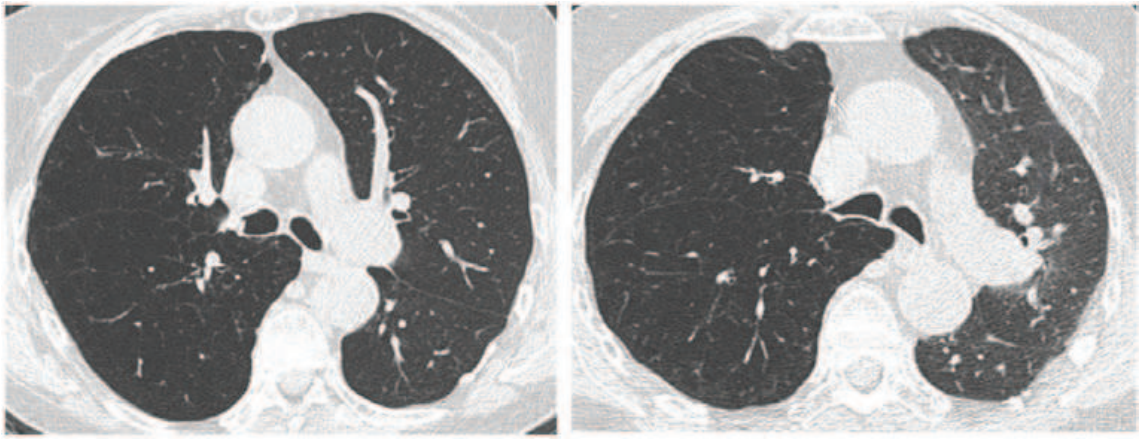
By applying the first method a patient with for example 49% (score 2) emphysema in the left upper lobe and 52% (score 3) in the lower lobe is called 'heterogeneous' (3 minus 2 = 1 point difference). The same patient is called 'homogeneous' when the second method is used (52% minus 49% = 3%). This example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

Hyperinflation

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

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

Inspiration **Expiration**



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

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

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

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

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

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

Surgical treatments

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

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

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

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

New bronchoscopic treatment modalities

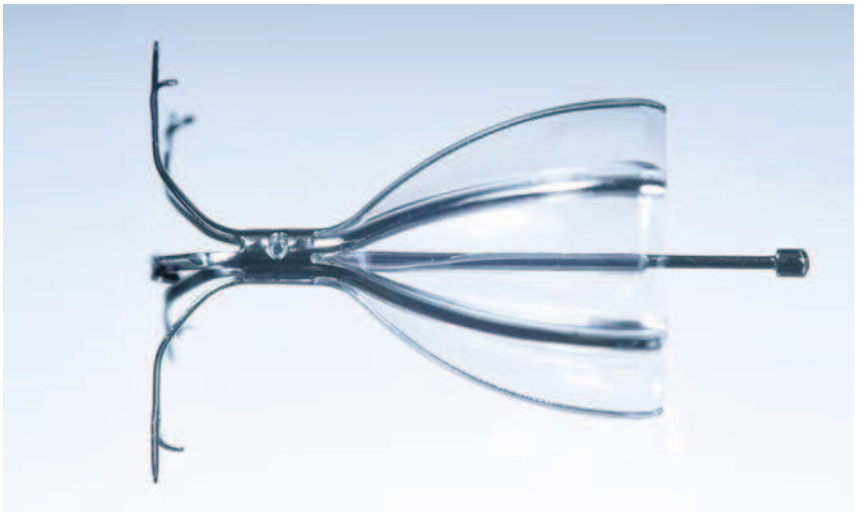
Bronchoscopic treatments
In the last decade several novel bronchoscopic treatments have been developed and are currently under investigation. These innovative bronchoscopic approaches are much less invasive compared to surgical treatments and might be applicable in a greater population of patients with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

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

Intra bronchial valve

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

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



Endobronchial valve

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

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

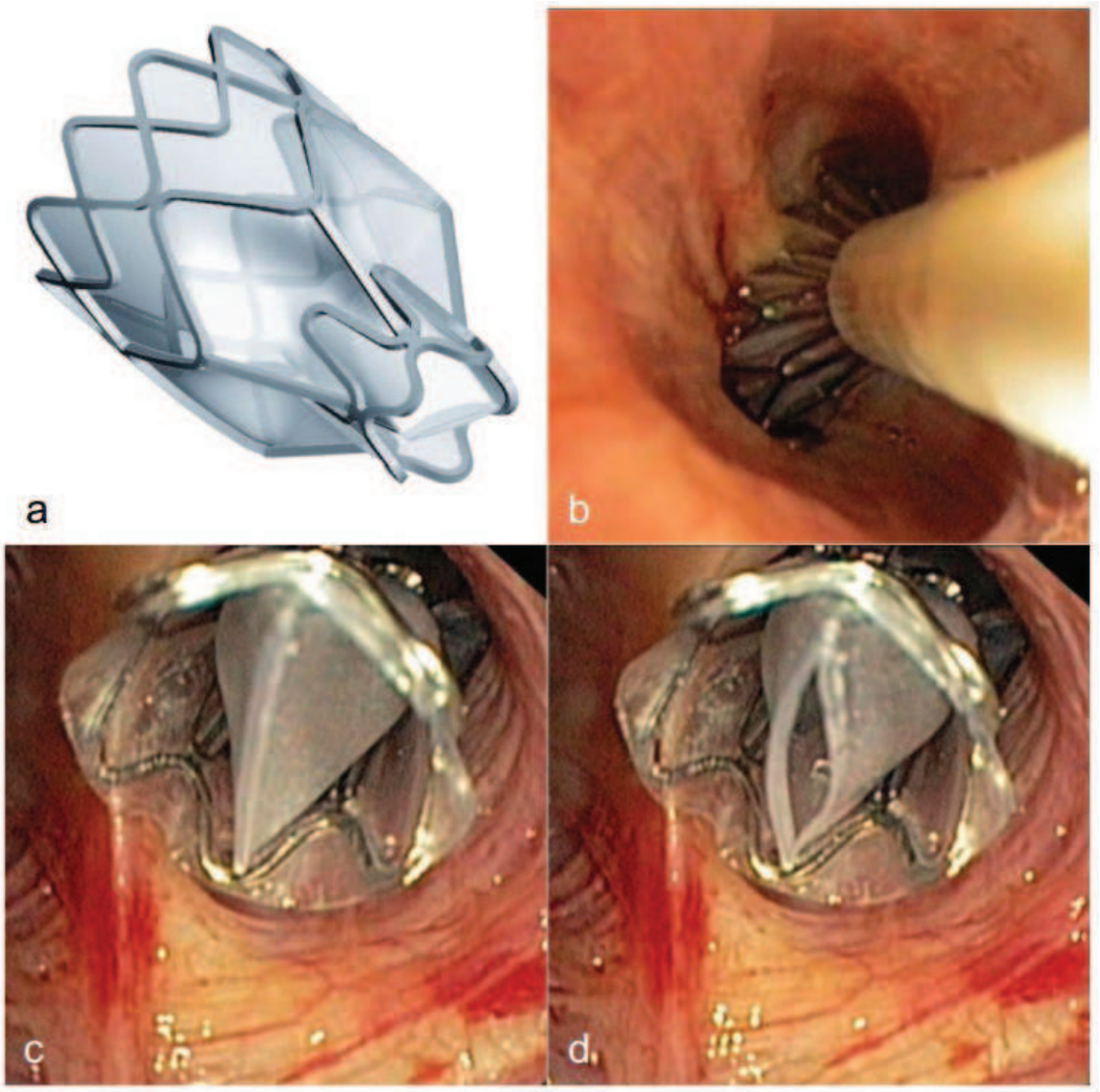
Endobronchial valve (Zephyr© Pulmonx Corporation, Redwood City, California, USA).

Endobronchial valve, 3 sizes
4.0 LP, 4.0 and 5.5

Loading cartridge

Delivery cathether

Bronchoscopic view of the endobronchial valve.[40]



(a) Endobronchial valve, cartoon

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

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

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

Fissure analysis and measurement of collateral ventilation

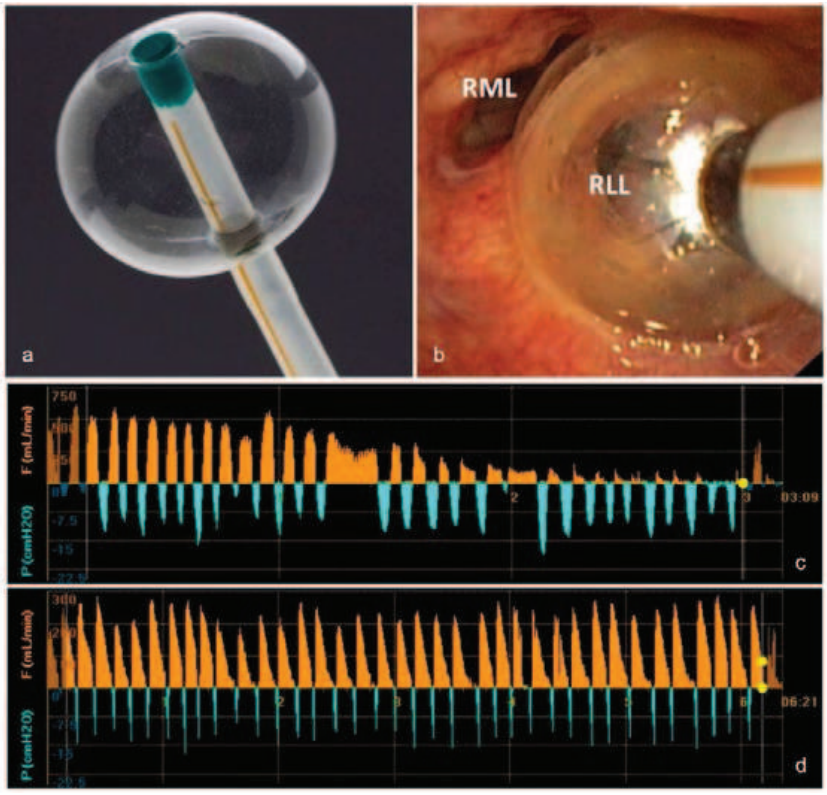
As indicated, to achieve lung volume reduction it is crucial that there is absence of collateral ventilation between the target lobe and the adjacent lobe. While it was originally thought that airflow into and out of a lobe occurs only via the airways feeding the segment to that lobe, in 1930 van Allen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

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

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

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

Representation of a Chartis measurement. [40]



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

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

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

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

Bronchoscopic lung volume reduction coil treatment

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

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

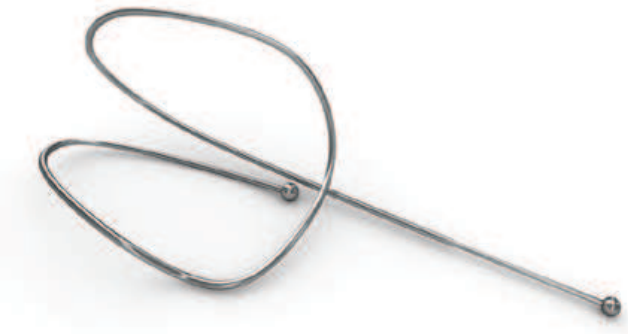
The components of the RePneu® Coil System.

Catheter

Forceps

Cartridge

Guidewire



Coil

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

Aims and outline of this thesis

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

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

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

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

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

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

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

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

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

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

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